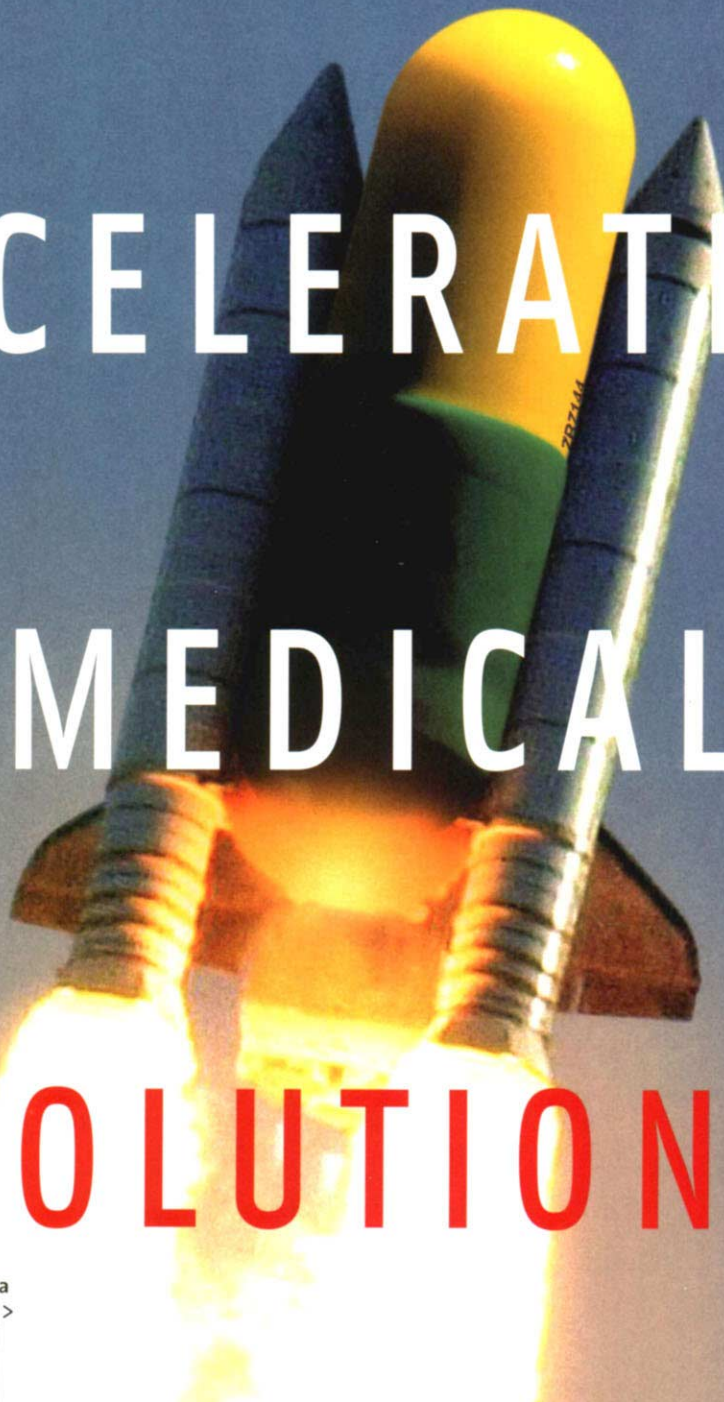


THE MILKEN INSTITUTE

Review

FIRST QUARTER 2004

A JOURNAL OF ECONOMIC POLICY



ACCELERATING MEDICAL SOLUTIONS

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Michael L. Klowden, *President and CEO*

Michael Milken, *Chairman*

PUBLISHER

Joel Kurtzman

EDITOR IN CHIEF

Peter Passell

ART DIRECTOR

Joannah Ralston, *Insight Design*

MANAGING EDITOR

Larry Yu

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Requests for additional copies
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The Milken Institute
The Milken Institute Review
1250 Fourth Street, Second Floor
Santa Monica, CA 90401-1353
310-570-4600 telephone
310-570-4627 fax
info@milkeninstitute.org
www.milkeninstitute.org

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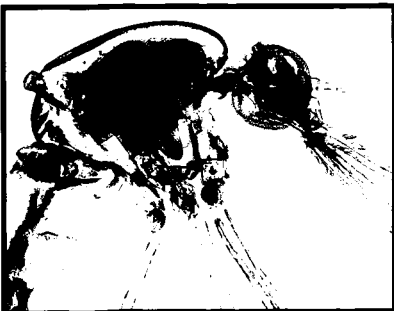
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Millions of lives, billions of dollars.

*by F. Desmond McCarthy, Holger Wolf
and Yi Wu*

In a 1995 speech at the National Cancer Summit, I proposed a 10-point action program to speed up the War on Cancer. Some of these points and other similar proposals have been incorporated in the “Roadmap for Medical Research” announced last fall by the National Institutes of Health. This roadmap, along with recent changes at the Food and Drug Administration, are positive steps. But much more needs to be done to optimize the infrastructure of medical research and treatment.

That’s why this issue of the *Milken Institute Review* is important. It covers life-and-death matters that will affect each of you and your families, and it shows how you can become involved through a new organization, the Center for Accelerating Medical Solutions (CAMS). Recognizing that all of us have or will someday have a serious disease, CAMS is focused on what it will take to cure those diseases *in your lifetime*.

Despite some important breakthroughs, progress in medicine has not matched the advances in other areas of science and technology. Telescopes in space have brought us closer to unraveling the origins of the universe even as the genome project has brought us closer to unraveling the mysteries of the cell. The cost of sequencing a gene has fallen from more than \$100 million in 1974 to less than \$6. Today, the cell phones we carry in our pockets contain the data equivalent of the world’s largest computers of the 1970s. A child’s toy contains more processing power than the lunar module that landed in 1969.

In our economic life, technology has helped bring home ownership within the reach of 70 percent of Americans. More than half of us own stock. Productivity has leapt

forward – a factory worker earns enough in a single day to fly across the country, a fact that would have astounded those of our forebears who risked their lives and fortunes for months in covered wagons.

In 1900, one of every five American babies died within five years. Wealth and power afforded no protection against tragedy – 16 U.S. presidents have lost a child in infancy. But in the last 100 years, our progress against infant mortality, infectious diseases and cardiovascular disorders has extended life expectancy by a remarkable 54 percent. There has also been progress against cancer. For example, cure rates for childhood leukemia have improved from about 5 percent to more than 80 percent and new treatments for testicular cancer are often highly effective. Just ask five-time Tour de France winner Lance Armstrong.

Unfortunately, progress against many of our most serious diseases has been slower. An American man still has a one-in-two chance of developing cancer; a woman’s chances are one-in-three. Alzheimer’s, diabetes, kidney diseases, AIDS and other serious conditions continue to devastate individuals and families.

Everyone focused on finding better treat-

ments and cures – patient advocacy groups, scientists and doctors at medical research centers, biotechnology and pharmaceutical company researchers, government officials and foundation executives – sincerely wants to strike down deadly conditions faster. The problem is that they face a maze of conflicting incentives, often-outdated regulations and other roadblocks to progress.

Thirty-two years ago, when I first began to focus on medical research programs, the conventional view was that if you poured enough money into research aimed at a single medical problem, you'd eventually find a single solution. This is the "magic bullet" theory. Penicillin had been a magic bullet for bacterial infections; the Salk vaccine for polio. Surely, it seemed then, a pill to cure breast cancer was just around the corner.

Over the past generation, the medical research community has become far more sophisticated in understanding the cellular basis of disease. Advances in molecular biology, genomics, imaging, information processing and other areas of science have helped us to formulate the great questions of medicine with growing precision. Having interacted with thousands of dedicated physicians and scientists over three decades, I'm convinced we have the talent and other resources to begin finding answers to those questions. But the recent death from cancer of *Wall Street Journal* editor emeritus and CAMS board member Robert Bartley, one of the great journalists of our time, is just one more reminder that we're not finding the answers fast enough.

With its non-partisan focus on human capital and economic incentives, the Milken Institute is ideally positioned to approach this issue creatively. Last year, we established the Center for Accelerating Medical Solutions under the auspices of the Institute with the goal of developing a better approach to solving

medical problems. While CAMS will not conduct medical research, it will make concrete proposals on how we can better coordinate worldwide medical resources, improve medical education, accelerate the application of technology to medicine, eliminate unnecessarily restrictive regulation, move products to the marketplace faster, recruit more of the brightest students to research careers, increase participation of patients in clinical trials, encourage public and private investment in developing new treatments, and much more.

Information about how you can become involved with CAMS is at www.fastercures.org.



Michael Milken

Michael Milken
Chairman

Welcome

to a very special edition of the *Milken Institute Review*.



In recent years, the Milken Institute has focused on the economic issues related to health care.

Last summer, we launched our newest initiative, the Center for Accelerating Medical Solutions (CAMS), whose mission is to save lives by saving time in the discovery and development of new and effective treatments for deadly and debilitating diseases.

In furtherance of this mission, we have assembled a talented executive team and a distinguished board of directors, with leaders in health care, business, public policy and science. It also includes two Nobel laureates – David Baltimore, president of the California Institute of Technology, whose short essay on engineering immunity begins on page 93, and Gary Becker, professor of economics and sociology at the University of Chicago.

Other board members are Dr. Ernest Bates, a board-certified neurosurgeon, chairman and CEO of American Shared Hospital Services, and vice chairman of the Board of Trustees of Johns Hopkins University; Richard B. Brewer, president of the biopharmaceutical company Scios Inc.; Nancy Brinker, former U.S. ambassador to Hungary and founder of the Susan G. Komen Breast Cancer Foundation; Dr. Gerald Levey, provost and dean of the UCLA

School of Medicine; Peter May, director, president and COO of Triarc Companies, and chairman of the Board of Trustees of the Mt. Sinai Medical Center in New York City; Shmuel Meitar, a leading Israeli businessman and long-term supporter of medical research; Dr. Richard Merkin, CEO and founder of Heritage Provider Network and one of America's most innovative thinkers in working to make the health care payment system more efficient; and Michael Milken, chairman of the Milken Institute and CAMS.

We mourn the loss of board member Robert Bartley, editor emeritus of *The Wall Street Journal* and Pulitzer Prize winner, who died in December.

Because of the importance of CAMS's mission, Peter Passell, editor of the *Review*, Greg Simon, president of CAMS, and I decided to do something we have never done in the history of the *Review*: devote an entire issue to one subject.

In the pages that follow, you will read more about the mission of CAMS. By focusing this *Review* to these topics, we hope to advance the debate about these important issues, and hope you'll join us in this effort.

A handwritten signature in black ink, reading "Mike Klowden".

Michael L. Klowden
President and CEO

Why We Suffer

the *Milken Institute Review*

– “A Journal of Economic Policy” –
devoting this issue to the topic of
accelerating medical solutions? What
does the effort to develop cures for
diseases have to do with economics?
Read a few of the articles – for in-
stance, **Desmond McCarthy**, **Holger**

Wolf and **Yi Wu** discussing how much eradicating malaria would increase output in
desperately poor parts of Africa – and you’ll see the linkage. Expect to see more
provocative articles related to the work of the Center for Accelerating Medical Solu-
tions (CAMS) in future editions of the *Review*.

CAMS is an “action tank” devoted to sav-
ing lives by saving time in the discovery, clin-
ical development and distribution of effective
treatments for our most deadly and debilitat-
ing diseases. We are nonpartisan, nonprofit
and independent of interest groups – except,
of course, the group eager to reduce human
suffering.

To make the leap from cost to benefit,
economists often translate the value of a life
into dollars by observing how much people
are willing to pay to reduce the risk of death
by a small amount – say, by purchasing car-
bon monoxide alarms for their homes or
demanding an extra \$5 an hour to work in an
explosives factory. The numbers are, at a bare
minimum, \$25,000 per life-year. Yet, as **Frank**



Lichtenberg of the Columbia University Busi-
ness School estimates in these pages, the aver-
age new drug saves 11,200 life-years each and
every year. Assuming this average drug costs
about \$700 million to develop, the annual
rate of return on a dollar spent on drug R&D
is an astounding 40 percent.

At CAMS, we also focus on the economics
and structure of the system for developing
medical solutions. To understand such prob-
lems, think of a train traveling between Wash-
ington DC and New York. The old trains take
three hours. The new ones could cover the
distance in two hours – but the tracks are not
up to the task so they must poke along at
speeds that save just 15 minutes. At CAMS we
are focusing on building better tracks for all



the new “trains” being designed by scientists to fight a variety of diseases.

Several of our authors address the problems of the health care marketplace – and ways to build faster tracks – from different perspectives. **Jenny Lanjouw** of the Brookings Institution offers a plan for opening poor countries’ markets to generic drugs without undermining patent rights in rich countries. **Paul Pecorino** of the University of Alabama Business School assays the impact of reimporting pharmaceuticals from Canada, while **Lawton Burns** and **Patricia Danzon** of the Wharton School analyze distribution channels for drugs. **Richard Foster** of McKinsey & Co. uses insights from the evolution of the electronics industry to project changes in the pharmaceutical industry that will affect efficiency of the industry’s innovation machinery.

CAMS will examine the efficiency of our research enterprise and the effectiveness of public and private funding of research. Harvard’s **Michael Kremer** shows the importance of

this approach by explaining how changes in the way medical research is subsidized could speed innovation in vaccines aimed at poor countries. **Mark McClellan**, commissioner of the FDA, outlines the case for more equitable sharing internationally of the R&D costs of drug development, while **Iain Cockburn** of Boston University looks more closely at the nuts and bolts of burden sharing.

CAMS will also review the barriers to improving the speed and success of clinical trials. **Steven Walker** of the Abigail Alliance for Better Access to Developmental Drugs and **Dan Popeo** of the Washington Legal Foundation explain how FDA rules prevent terminally ill patients from using experimental pharmaceuticals and address the difficult issues surrounding the “compassionate use” of experimental drugs.

Perhaps most important, CAMS will be a catalyst for change in the way we address and conquer the diseases of our day. Nobel Prize-winning scientist – and CAMS board member – **David Baltimore** points out that we need revolutionary new approaches to boosting our immune systems if we are to prevail against some of the most deadly and intractable diseases.

Why cover accelerating medical solutions in an economic journal? If economics is the study of how we value various aspects and activities of life and communicate that value, what could be of more economic importance than extending life itself?



Gregory C. Simon

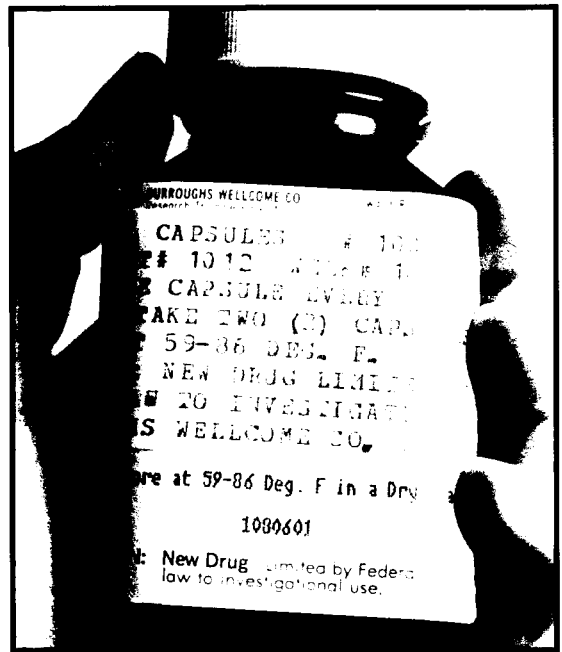
Greg Simon, President
Center for Accelerating Medical Solutions

BY STEVEN WALKER AND DAN POPEO

David Baxter, a high school student in Woodland, Calif., was diagnosed with colorectal cancer in the spring of 2001. David was unable to participate in clinical trials of promising new drugs because such trials are usually closed to patients under 18. He died in October, 2001, shortly after his 17th birthday.

Alita Randazzo, a 35-year-old woman who worked in her father's tavern in southern New Jersey, was diagnosed with colorectal cancer in the spring of 2000. She responded well at first to a new drug called Eloxatin, but had to endure the expense and demands of traveling to France to get it. The drug was still undergoing clinical trials in the United States and Ms. Randazzo did not qualify. After eight months, Eloxatin stopped helping her and her doctors believed her last chance was the drug Erbitux, which was also still in clinical trials. She was unable to obtain Erbitux and died on July 20, 2002.

David and Alita are just two of the hundreds of thousands of Americans who have fallen into a little discussed, but often fatal, gap in the United States health care system: their disease could not be treated effectively by any approved therapy, and FDA policy generally bars individual access to drugs still in development. As the introduction of drugs has been accelerating – the FDA received



2,374 applications for clinical tests last year, compared with 1,596 in 1986 – this gap in the availability of potentially effective drugs for the terminally ill is likely to widen. That is, unless current policies change.

INSIDE DRUG DEVELOPMENT

To understand what's happening, consider the tortuous birth of a drug from a regulatory perspective. New drugs for serious diseases are first identified when a substance shows

STEVEN WALKER is an adviser to the Abigail Alliance for Better Access to Developmental Drugs. **DAN POPEO** is chairman and general counsel of the Washington Legal Foundation.

TRENDS

activity against a medical condition in laboratory bench and animal testing – for example, in a culture of cancer cells or in mice. In some cases, the agents are found by screening hundreds or thousands of compounds. Increasingly, though, drugs are being created to deal with molecular targets believed to be the causes of disease. In all these cases, initial development in the laboratory is called the preclinical phase.

Drugs showing promise are then moved into the clinical phase of development, and direct FDA regulation begins. The sponsor of the trials, usually a pharmaceutical company, must submit an Investigational New Drug (IND) application to the FDA before providing the drug to any patient. The IND application includes information about the preclinical testing and the protocol that will first be used in administering the drug to humans. The FDA may approve or deny the IND, or request additional information. Upon acceptance of the IND, the FDA will allow testing of the drug to hundreds or even thousands of patients.

The first tests in humans are known as Phase I clinical trials, and generally enroll between 20 and 80 patients. The tests are usually limited to determining safe doses, identifying side effects and gathering early evidence of efficacy. The Phase I data is used to decide whether the drug is safe enough to test further, and sometimes to select the disease(s) the drug is most likely to treat successfully. Phase II clinical trials are conducted to further test the efficacy of the drug. Phase II trials enroll up to several hundred patients and take from one to several years to complete. In some cases, FDA approval can be sought based on Phase II data.

Phase III clinical trials are the final step prior to approval. These late-phase trials in-

volve hundreds to thousands of patients and can take several years. The primary goal is generally to determine whether the new treatment is better than an already-approved treatment. Patients are usually assigned randomly to groups receiving different treatments for purposes of comparing outcomes.

Before starting any clinical trial, the sponsor must submit a protocol to the FDA for review and receive approval from an Institutional Review Board. When the sponsor believes that enough data has been collected to support approval, a New Drug Application is submitted for review. Applications for biologic drugs like vaccines or monoclonal antibodies are called Biologics License Applications. The application must contain data from preclinical and clinical testing including evidence of safety and efficacy, how it will be administered, significant side effects and risks, pharmacology and other information.

The FDA will not evaluate a new treatment until the data is submitted in an application, thus ensuring that the agency is the last to know that an important treatment has emerged. The FDA first decides whether to review the application at all, then usually completes its initial review within 6 to 10 months. Based on the review, the FDA can issue an approval, request more information (thus delaying the final decision), or deny approval.

At each phase of the trials, considerable time passes as the drug's sponsor obtains FDA approval of the proposed study protocols, as investigators carry out the trials and as the sponsor obtains FDA approval or rejection of the results at each stage. According to the Tufts Center for the Study of Drug Development, the total time for trials and approvals for a new drug in the United States averages 6.9 years.

While clinical trials are in progress, infor-

mation regarding the safety and efficacy of the drug is continually emerging. A drug may be believed to be active or even dramatically effective as early as Phase I, and the news of particularly promising ones spreads quickly through the medical community. Nonetheless, the drug remains available only to the few who are fortunate enough to gain access to clinical trials – though exceptions are sometimes made for compassionate use on a small scale.

The FDA can grant accelerated approval for a drug intended to treat a life-threatening disease with unmet needs, based on data from a Phase II trial. The idea is to allow earlier marketing of drugs for serious diseases, based on limited evidence from surrogate endpoints (e.g., control or regression of tumors) that the drug will eventually meet the requirements for regular approval. But in practice, accelerated approval has been a limited success. Among other problems, the program has proven to be a high-risk option for sponsors, requiring post-approval clinical trials that are difficult to complete.

Regular approval is based on endpoints (e.g., overall survival) that are, in the opinion of the FDA, less equivocal than surrogate endpoints. Sponsors that receive regular approval are generally not required to conduct additional clinical trials for the approved indication. Marketing under either approval mechanism is unrestricted.

The FDA's policies governing the design and conduct of clinical trials are almost exclusively intended to generate data suitable for statistical analysis. The emphasis on statistics as the primary tool for decision making means that the clinical trials must be very



tightly controlled, with strict entry and exclusion criteria. The statistical methods used by the FDA can handle only apples-to-apples comparisons, so the patients in a study must be as alike as possible with regard to their condition. Consequently, trials designed in accordance with FDA requirements can address only narrowly defined questions in small cross sections of patient populations.

The FDA's approach and the enormous expense of clinical trials also causes sponsors to design drug-development programs aimed at an approval for a single indication within a single disease. This leads to a limited number of trials along a straight-line path toward approval. The trials are large enough to generate valid statistical data – but no larger. Larger trials would take longer to enroll, and complete, and would cost more. Once the drug is approved for a single indication, it can

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be prescribed for any other, creating an obvious incentive to pursue the most focused approval strategy possible.

The result is a system that does not work well for the FDA or the industry – and one that rarely works at all for patients who have no options for extending their own lives other than investigational drugs. The FDA's regulations have been designed to control the marketing of medical treatments, and to make the process orderly for the agency. This traditional regulatory approach has had the unintended consequence of erecting virtually insurmountable barriers between the developers of new treatments, and the patients who need them. Hundreds of thousands of terminally ill Americans find themselves with no remaining approved treatment options and no access to promising drugs.

In response to activism by advocates for HIV/AIDs patients in the early 1990s, the FDA and Congress created several new policies under the IND process to allow access to investigational drugs outside regular clinical trials. These policies include single-patient INDs, treatment INDs and open-label protocols. All are forms of clinical trials that are closely regulated by the FDA. The single-patient IND allows a physician to treat a single patient with an investigational drug if the sponsor agrees to provide the drug. The sponsor and physician must submit extensive paperwork. The FDA reviews each request separately – a cumbersome process generally acknowledged as workable only for small numbers of desperate patients.

The treatment IND and open-label clinical trial protocol are designed to allow treatment of larger numbers of patients under a single protocol and, in the case of a treatment IND, theoretically allows the sponsor to recover some of its costs by charging patients. Investi-

gational drugs have been provided to patients under these policies. But due to economic and regulatory disincentives, these types of access programs are exceedingly rare. And the ones that have been established have had restrictive entry criteria similar to those that limit access to clinical trials.

ERBITUX: A CASE STUDY IN REGULATORY TRAGEDY

According to the American Cancer Society, colorectal cancer will kill some 57,000 in the United States this year. Among all cancers, only lung cancer will kill more Americans. Erbitux, which is widely viewed as a safe and effective breakthrough drug for colorectal cancer, has traveled a tortuous regulatory path and remains unapproved in the United States. Yet convincing evidence that Erbitux dramatically helped colorectal cancer patients live longer and better lives was emerging long before the drug became the center of an FDA rejection. That rejection, incidentally, spawned the insider-stock-trading scandal that led to the indictment of Martha Stewart.

The little-covered angle to the story is that the FDA's inflexible policies were arguably the single most significant factor leading the agency to reject the ImClone Corporation's first application for approval of Erbitux in December 2001. Few of the patients who would likely have benefited from Erbitux at that time remain alive today.

It is widely assumed that FDA was forced to send ImClone back for more trials. But in truth, the decision was a judgment call that has since proved to have been a very poor one. The rejection stalled the development program of an extremely promising new drug and steered it into a regulatory traffic jam with Eloxatin, another effective drug for colorectal cancer that had been delayed by its own ill-considered rejection in 2000.

The Phase II trials for Erbitux were intended to test the drug for second-line treatment of colorectal cancer, meaning it would be used to treat patients who had failed to benefit from current standard care. The Phase II trials were not originally intended to support approval. But ImClone decided to go forward with what it had, believing the FDA would

from scratch with a trial that would be more complex and would take longer.

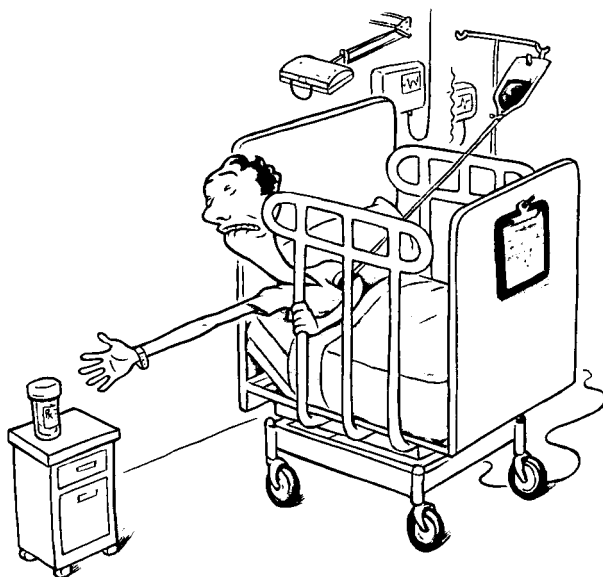
Among other problems, the retesting of Erbitux would need to wait for Eloxatin to be available so the new trials for Erbitux would have a population of patients fitting the entry criteria. Thus, nobody got access to Erbitux again in the United States until August 2002,

The traditional regulatory approach has had the unintended consequence of erecting virtually insurmountable barriers between the sponsors who are developing the new treatments, and the patients who need them.

approve the drug because it worked in some patients who had no other options.

This is the situation that accelerated approval was created to handle, and ImClone requested approval under that authority. In rejecting the application at the 11th hour, the FDA cited problems with the trial designs, conduct and reporting. ImClone's interpretation of the trial results would later be confirmed in other trials, but FDA officials claimed at the time that they could make nothing of the data.

With the rejection, ImClone and its partner, Bristol-Myers Squibb, lost their place in line for review to Eloxatin. The word among oncologists was that results in the Eloxatin trials would probably be good enough for approval as the second-line therapy for colorectal cancer. And if Eloxatin did make the cut, Erbitux's only chance to be eligible for accelerated approval would be as a third-line treatment for patients (like Ms. Randazzo) who had failed to benefit from either the Saltz regimen or Eloxatin. And that meant starting



when a clinical trial with a few hundred terribly sick patients was started. Meanwhile, trials by ImClone's European partner, Merck KGaA, were underway, and the oncology community hoped that those results might be used to support a new application for approval on this side of the Atlantic.

The House Energy and Commerce Committee held hearings on the matter in 2002.

TRENDS

The committee revealed – and ImClone confirmed – that the company had made errors in its clinical trials. ImClone officials apologized and vowed to continue developing the drug as quickly as they could. For their part, FDA officials were evasive and unapologetic, but did say that they had considered their action a rejection of the application – not of the drug itself. The committee concluded that

cal to those found by ImClone in 2001. ImClone and Bristol-Myers Squibb submitted their second application for approval in August 2003. The results of the initial trials rejected by the FDA were reconfirmed. And it now seems clear that the FDA's handling of the ImClone application was a tragic error. The error, we believe, is not an isolated instance but rather a high-profile example of systemic failure yet to be corrected.

For patients who are dying, a policy that withholds promising drugs during the lengthy review process is overkill – literally.

communications by the FDA could have been more effective at critical points in the process – a finding that eventually led to the merger of two FDA drug-review divisions.

But the committee only scraped the surface of the problems exposed by the Erbitux tragedy, and appeared to have been utterly unaware that the drug actually worked well for some terminally ill patients. Congress has done nothing since the hearings to push the agency toward better performance.

In February 2003, under pressure from patient advocates, ImClone and Bristol-Myers Squibb opened an expanded access program under one of the FDA's existing mechanisms. The program uses a waiting list and lottery for enrollment of patients who cannot get the drug through a clinical trial. The program was set up to accommodate fewer patients than were seeking the drug. But the companies have provided the drug at no cost to patients enrolled, and appear to have increased the number being admitted. Many continue to wait, though, and some die waiting.

In May 2003, the results of the European trials were announced and were nearly identi-

By its own rules, the FDA must decide whether it will approve Erbitux by mid-February 2004. And as this is being written, the agency is showing no sign that it intends to beat that schedule. This American-invented drug is now approved in Switzerland, and will likely be approved in other European countries before it is made available to American patients. In the meantime, some 150 Americans will die each day from colorectal cancer.

The tragedy is not limited to colorectal cancer patients. Erbitux blocks a protein, epidermal growth factor receptor, known to be active in the progression of a number of other solid-tumor cancers, including lung cancer. No patients suffering from any of these other deadly cancers have been able to gain access to Erbitux because of the restrictions imposed on sponsors by the FDA.

Although the FDA has created programs to allow some access to unapproved drugs, the programs do not cede enough control to those in the best position to make decisions for patients facing death: the patients themselves, in consultation with their physicians. The FDA's access programs also impose sig-

nificant disincentives on sponsors to pursue the programs. Hence, they are rare, generally small, and offered only when approval of the drug is expected shortly. The result is a system that does not work for the majority of seriously ill patients who are beyond help from approved treatment options.

A SOLUTION: TIER 1 INITIAL APPROVAL

Underlying the systemic failure is the fact that FDA regulations fail to recognize that patients have different risk-benefit trade-offs. Plainly, many patients who are terminally ill and who have no other treatment options are willing to take their chances with promising drugs that have yet to run the regulatory gauntlet. Extensive marshalling of evidence regarding drug interactions, dose optimization and the like, as well as studies of sufficient size to yield a high statistical confidence level regarding efficacy, are appropriate for new drugs to treat patients with therapeutic alternatives. For dying patients, however, a policy that withholds promising drugs during the review process is overkill – literally. Such patients should have easy access to treatment that has met a lower evidentiary hurdle.

The Abigail Alliance for Better Access to Developmental Drugs, a patient-advocacy group based in Arlington, Va., and the Washington Legal Foundation, a nonprofit public-interest law and policy center in Washington, have proposed that the FDA adopt a program for allowing this early access.* The program, “Tier 1 Initial Approval,” would enable the FDA to grant limited approval for promising drugs based on early evidence of effectiveness and safety. Drugs receiving Tier 1 Initial Approval could be sold only to the terminally ill. To prevent disruption to clinical trials that could lead to full approval of a drug, patients would only be eligible for access to drugs under Tier 1 Initial Approval if they had been

denied participation in a clinical trial for the drug, or if their physicians had determined that the patients were not reasonable candidates for a clinical trial – for example, by reason of geography or prior treatment history.

The two organizations have also filed suit against the FDA on behalf of patients seeking investigational drugs. The lawsuit argues that the agency’s present policies amount to an unconstitutional deprivation of life and liberty without due process.

The FDA has the power to fix the policies on its own, since its mandate from Congress to regulate drug efficacy is couched in very general terms. For full marketing approval, the Food, Drug and Cosmetic Act simply requires “substantial evidence that the drug will have the effect it purports or is represented to have.” Substantial evidence is not defined in terms of a specific methodology, but as “adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have.” Early evidence of efficacy in clinical trials could be the substantial evidence that the FDA needs to justify approval on a limited basis.

Ultimately, the issue is not so much legal as philosophical: how much leeway are we willing to give patients and their doctors to make their own decisions regarding drug use when the evidence is uncertain? How much autonomy should dying patients have? The U.S. Supreme Court has said that mentally competent patients who are dying have the right to refuse treatment – to choose death. Shouldn’t they also have the right to choose life? ■

**As noted above, the authors are affiliated with these two organizations.*

HIV/AIDS does not yet hold the undisputed crown as the Third World's most devastating disease. But as these 2010 projections made by the U.S. Census for the U.S. Agency for International Development suggest, that dubious honor is well within reach.

Africa, as is widely known, is at great risk. But few understand just how appalling the pandemic could become without more effective containment. South Africa, the economic locomotive of southern Africa, faces a 32-year cut in life expectancy – back to levels last experienced in Europe in the 18th century. Swaziland, South Africa's *de facto* dependent, tops the misery charts at a dispiriting 41.6-year decline in life expectancy.

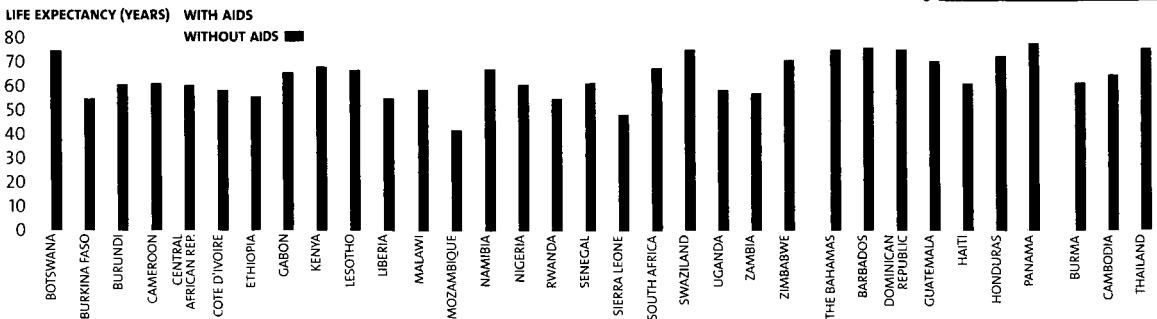
The figures for the numbers of children likely to die before the age of five are equally wrenching. For example, early childhood mortality will be more than twice as high as the baseline figure in South Africa. And in Botswana, a country that has otherwise led southern Africa in public health gains, AIDS will increase childhood mortality by a factor of six.

Central America and the Caribbean are doing considerably better than Africa, and Asia is ahead of Central America. But note that two Asian countries not listed here – India and China – face steeply rising incidences of HIV/AIDS. And even if the disease is contained in the next decade, the absolute numbers of victims will be enormous, simply because so many people live there.

— Peter Passell

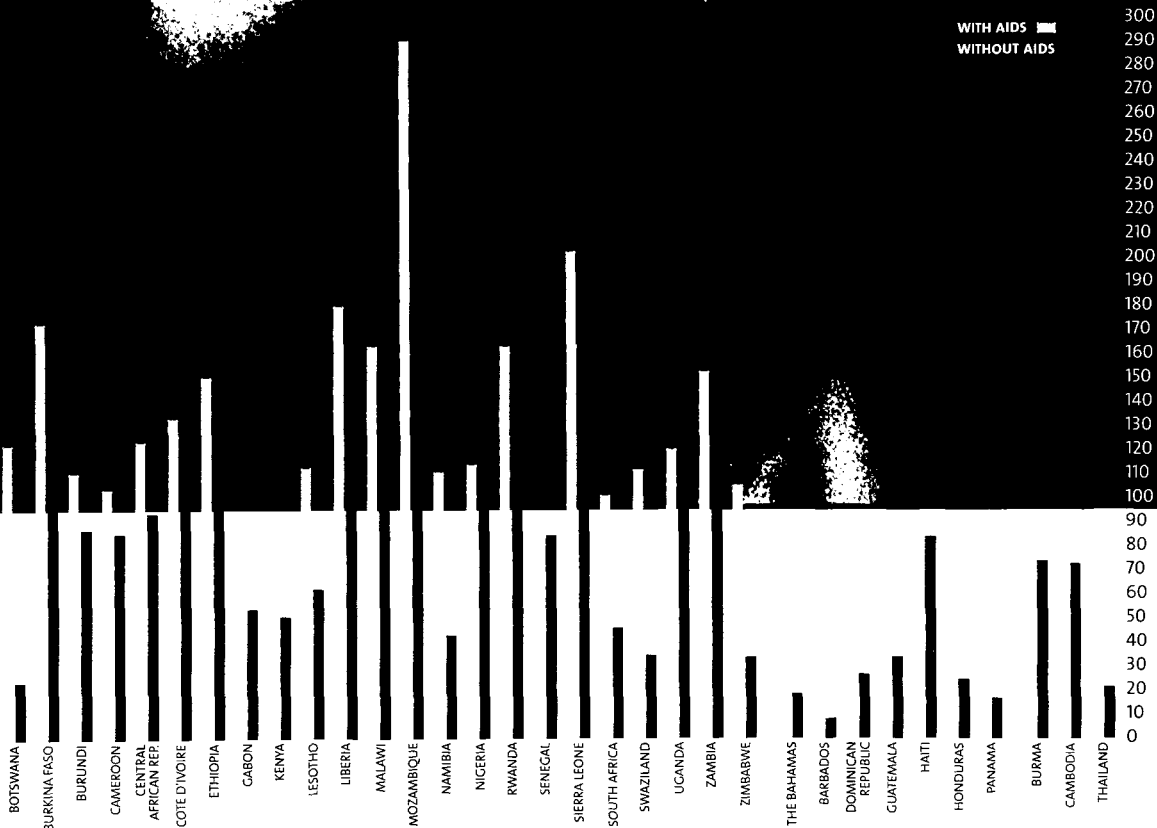
DEMOGRAPHIC CHARACTERISTICS WITH AND WITHOUT AIDS: 2010

SOURCE: U.S. Census, prepared for US AID



GETTY IMAGES

CHILD MORTALITY (MORTALITY RATE OF CHILDREN UNDER AGE 5 PER 1,000 LIVE BIRTHS)



By Frank R. Lichtenberg

[Longer]

Through

In recent years, economists have generally accepted the idea that traditional measures of economic growth significantly understate the true growth rate. One reason is that GDP statistics do not account for important intangible benefits of modern life – notably, increased leisure, better health and longer life. Consider longevity. The average person born in 1995 can expect to live a remarkable 22 years longer than his or her counterpart born in 1920.

Assaying the value of extended life spans may, on first reflection, seem a task for philosophers rather than economists. But many economic studies have leapt the conceptual gap by inferring how much people value their own lives from evidence of how much they are willing to spend for small increases in safety (say, by buying home smoke detectors) and how much they are



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willing to sacrifice in safety (say, by working in dangerous occupations like mining) in return for higher wages. Prof. William Nordhaus of Yale has argued persuasively that the underestimation of economic growth resulting from failure to translate increased longevity into GDP is substantial – that, adjusted for the value added by those extra years, the American economy grew twice as fast during the 20th century as the measured rate showed.

The forces driving increased longevity are not obvious. But there are clues in broader research on economic growth.

The work of the Nobel Prize-winning economist Robert Solow, which includes the most widely accepted theoretical analysis of economic growth, implies that technological progress has generated most of the gain in per-person income. And while early research assumed that the rate of technological progress was somehow determined from outside the system, more recent growth models recognize that technological progress depends on investment in research and development, and on the creation of new products and processes.

Indeed, there is abundant evidence that growth in conventionally defined per capita output is positively related to cumulative investments in research and development. For example, the manufacturing industries that invest most heavily in R&D generally have the highest rates of growth of output per worker. Here, I ask whether the unmeasured half of economic growth – the portion related to the increase in longevity – can also be explained by a specific sort of technological progress: the development and use of new drugs.

FRANK LICHTENBERG teaches economics at the Columbia Business School.

EARLIER EVIDENCE

The Pharmaceutical Research and Manufacturers Association, the industry trade group usually referred to as PhRMA, provides an anecdotal account of the contribution of drug innovation to medical progress in this century:

Antibiotics and vaccines played a major role in the near eradication of major diseases of the 1920s, including syphilis, diphtheria, whooping cough, measles and polio. Since 1920, the combined death rate from influenza and pneumonia has been reduced by 85 percent. Despite a recent resurgence of tuberculosis among the homeless and immunosuppressed populations, antibiotics have reduced the number of TB deaths to one-tenth the levels experienced in the 1960s. Before antibiotics, the typical TB patient was forced to spend three to four years in a sanitarium and faced a 30 to 50 percent chance of dying. Today, most patients can recover in 6 to 12 months if given the full and proper course of antibiotics.

Pharmaceutical discoveries since the 1950s have revolutionized therapy for chronic as well as acute conditions. From 1965 to 1995, cardiovascular drugs like anti-hypertensives, diuretics, beta blockers and ACE inhibitors drastically reduced deaths from hypertension, hypertensive heart disease and ischemic heart disease.

Similarly, H2 blockers, proton-pump inhibitors and combination therapies cut deaths from ulcers by more than 60 percent. Anti-inflammatory therapies and bronchodilators reduced deaths from emphysema by 31 percent and provided relief for those with asthma. Had no progress been made against disease between 1960 and 1990, roughly 335,000 more people would have died in 1990 alone.

Since 1960, vaccines have greatly reduced the incidence of childhood diseases – many of which once killed or disabled thousands of American children. Likewise, vaccines for hepatitis B introduced during the 1980s now protect a new generation of American children from a leading cause of liver disease.

Three economists, David Cutler, Mark McClellan and Joe Newhouse studied a single but very important pathology – heart attacks – by compiling results about the effect of various treatments on mortality. They found that changes in the medical treatments used in the management of myocardial infarctions (the most common form of heart attack) accounted for approximately 55 percent of the reduction in mortality that occurred in cases between 1975 and 1995, with the bulk of this improvement coming from pharmaceuticals. Three drug therapies – aspirin, thrombolytics and beta blockers – resulted in the largest gains. They also noted that “the long-term improvement in mortality may be even more substantial than the acute improvements.”

Many innovations have improved the treatment of patients with substantial damage to the heart from the attacks, including drug therapies like ACE inhibitors and anticoagulation therapy, but it is difficult to quantify

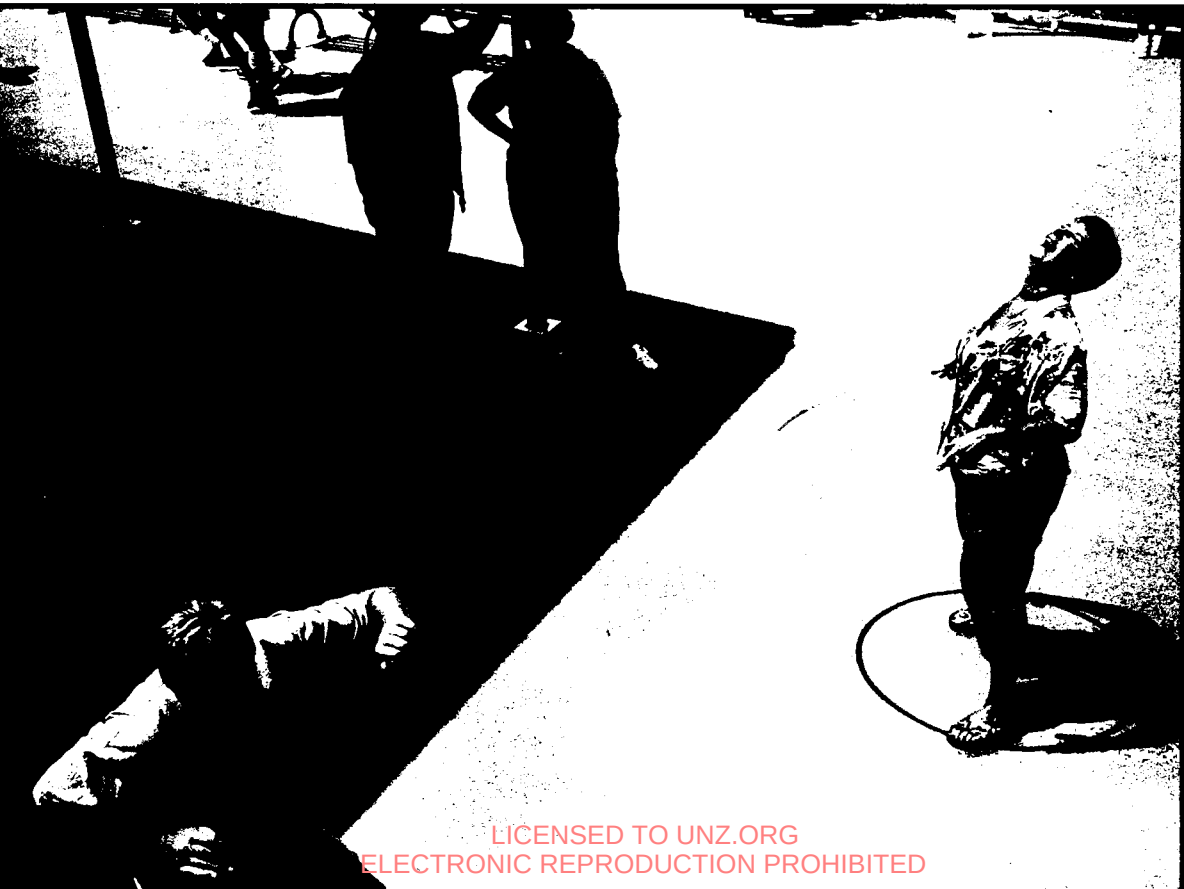
**NUMBER OF NEW MOLECULAR ENTITIES
APPROVED BY THE FDA**

PERIOD	FREQUENCY	PERCENT	CUMULATIVE FREQUENCY	CUMULATIVE PERCENT
1940-1944	2	0.18	3	0.27
1945-1949	11	0.98	14	1.25
1950-1954	116	10.37	130	11.62
1955-1959	142	12.69	272	24.31
1960-1964	100	8.94	372	33.24
1965-1969	53	4.74	425	37.98
1970-1974	81	7.24	506	45.22
1975-1979	92	8.22	598	53.44
1980-1984	98	8.76	696	62.2
1985-1989	106	9.47	802	71.67
1990-1994	114	10.19	916	81.86
1995-1999	177	15.82	1093	97.68

NOTE: Year of approval unknown for 15 new molecular entities.
Total does not add up to 100 percent due to rounding error.
SOURCE: Author's calculations, based on unpublished FDA data.

these important effects. The findings of Cutler, McClellan and Newhouse are especially provocative, since they observe, “the important question is whether [the] results generalize to other types of medical care.”

Two other economists, Ted Frech and



LONGER LIVING

Richard Miller, recently examined the relationship between pharmaceutical expenditures per capita and life expectancy, using data for 21 OECD countries. They found a significant positive relationship between drug outlays and life expectancy at age 40, and a



yet-stronger one at age 60. Note, however, that since older people tend to consume more drugs, it is difficult to untangle cause from effect: the correlation between drug use and life expectancy may reflect the effect of longevity on pharmaceutical expenditures, as well as the effect of pharmaceutical expenditure on life expectancy.

Clinical trials have provided a great deal of evidence about the impact of new drugs on mortality. One such study was the West of Scotland Coronary Prevention Study of some 6,600 ostensibly healthy men aged 45 through

64. The results indicated that the cholesterol-lowering drug pravastatin “reduces the risk of heart attack and death in a broad range of people, not just those with established heart disease, but also among those who are at risk for their first heart attack.”

Over five years, those healthy individuals treated with pravastatin “suffered 31 percent fewer nonfatal heart attacks and at least 28 percent fewer deaths from heart disease than a comparable group of men who received a placebo,” the study reported, adding, “in previous studies, pravastatin had been shown to reduce the risk of heart attack by 62 percent in patients with high cholesterol who already had heart disease.”

Evidence from clinical trials is of great scientific value, but some experts argue that the results cannot simply be extrapolated to real-world experience. Nor does there appear to be any way to combine the clinical-trial evidence in ways that shed light on the aggregate contribution of pharmaceutical innovation to mortality reduction.

GETTING TO THE NUMBERS

Estimating the impact of technological change is usually hampered by the lack of reliable data. In the case of drugs, however, it is possible to identify, date and classify every innovation since 1939 (because the industry has been strictly regulated by the FDA since that year), and to measure the rate of utilization of about 900 distinct drugs since 1980. The FDA supplied me with a list of all new drug approvals since 1939, along with other information about the drugs’ origins and use. This allowed a detailed inventory of pharmaceutical innovation during the last six decades.

I obtained data on market shares of indi-

vidual drugs from the 1980 and 1991 National Ambulatory Medical Care Surveys (NAMCS), which counted visits to doctors' offices, and the 1993 National Hospital Ambulatory Medical Care Survey (NHAMCS), which counted visits to hospitals' outpatient and emergency facilities. These surveys allowed me to estimate the number of prescriptions, by specific chemical, as well as by diagnosis, since 1980.

Almost half of some 1,100 new molecular entities that the FDA has approved since its inception were approved after 1980. It is therefore not surprising that the mix of prescribed drugs changed considerably between 1980 and 1994. Half of the drugs that were among the top 20 prescribed in 1980 were no longer in the top 20 by 1994. Similarly, half of the top 20 drugs in 1994 were not in the top 20 in 1980. Some of them, like the asthma reliever albuterol, had not yet been approved by the FDA in 1980.

I analyzed the relationship across diseases between the long-term reduction in life-years lost before age 75 and the relative utilization of new pharmaceutical products. In other words, I investigated whether there were above-average reductions in mortality from diseases for which there was above-average utilization of new drugs. Combining data from the FDA and the NAMCS, it is possible to calculate disease-specific measures of pharmaceutical innovation – that is, innovation relevant to each disease – since NAMCS reveals the use of each drug for each disease.

This approach controls for the effects of general trends – changes in wealth, nutrition and sanitation – that affect average mortality.

TOP 20 DRUGS PRESCRIBED IN DOCTOR-OFFICE VISITS IN 1980 AND 1994

RANK/DRUG	PERCENT OF PRESCRIPTIONS		CLASS
	1980	1994	
1980			
1. Hydrochlorothiazide	2.9	1.4	Diuretics
2. Aspirin	2.3	1.5	General Analgesics
3. Penicillin	1.9	•	Penicillins
4. Phenylpropanolamine	1.8	1.0	Nasal Decongestants
5. Alcohol	1.8	•	Antitussives, expectorants, mucolytics
6. Erythromycin	1.7	1.2	Erythromycins and lincosamides
7. Phenylephrine	1.7	1.0	Nasal decongestants
8. Acetaminophen	1.7	3.0	General analgesics
9. Codeine	1.5	0.9	Antitussives, expectorants, mucolytics
10. Tetracycline	1.4	•	Tetracyclines
11. Pseudoephedrine	1.4	•	Nasal decongestants
12. Riboflavin	1.3	•	Vitamins, minerals
13. Digoxin	1.3	1.1	Cardiac glycosides
14. Chlorpheniramine	1.3	•	Nasal decongestants
15. Ampicillin	1.3	•	Penicillins
16. Amoxicillin	1.2	3.8	Penicillins
17. Propranolol	1.2	•	Antihypertensive agents
18. Furosemide	1.1	1.2	Diuretics
19. Ergocalciferol	1.1	•	Vitamins, minerals
20. Neomycin	1.1	•	Ocular anti-infective and anti-inflammatory agents
1980 TOTAL	31.0		
1994			
1. Amoxicillin	1.2	3.8	Penicillins
2. Acetaminophen	1.7	3.0	General analgesics
3. Albuterol	•	1.6	Bronchodilators, antiasthmatics
4. Aspirin	2.3	1.5	General analgesics
5. Ibuprofen	•	1.4	Antiarthritics
6. Hydrochlorothiazide	2.9	1.4	Diuretics
7. Multivitamins, general	•	1.3	Vitamins, minerals
8. Furosemide	1.1	1.2	Diuretics
9. Erythromycin	1.7	1.2	Erythromycins and lincosamides
10. Guaifenesin	•	1.2	Antitussives, expectorants, mucolytics
11. Estrogens	•	1.1	Estrogens and progestins
12. Digoxin	1.3	1.1	Cardiac glycosides
13. Prednisone	•	1.1	Adrenal corticosteroids
14. Diltiazem	•	1.0	Antianginal agents
15. Beclomethasone	•	1.0	Unclassified
16. Phenylephrine	1.7	1.0	Nasal decongestants
17. Phenylpropanolamine	1.8	1.0	Nasal decongestants
18. Triamcinolone	•	0.9	Adrenal corticosteroids
19. Codeine	1.5	0.9	Antitussives, expectorants, mucolytics
20. Levothyroxine	•	0.9	Agents used to treat thyroid disease
1994 TOTAL	27.6		

NOTE: • indicates not in top 20 in that year.
Total estimated number of prescriptions was 899 million in 1980 and 921 million in 1994.

The analysis of mortality change in a cross-section of diseases is analogous to the analysis of output in a cross-section of industries. Industries produce goods, while diseases are “bads.” The pace of innovation varies across both industries and diseases, due in part to variation in technological opportunity.



I estimated the relationship between reductions in mortality and the introduction of new drugs for the entire period 1970-91 and for two sub-periods (1970-80 and 1980-91), as well as for different categories of disease, based on the average age at which people die from the disease. I also distinguished between drugs that the FDA says represent an advance over available therapy and what have been called “me-too” drugs. The data cover all diseases and all drugs used by patients outside hospitals, thus making it possible to draw general conclusions about the impact of new drugs on longevity – conclusions that could not be drawn from previous studies that focused on specific diseases and/or drugs.

MODELING THE IMPACT OF NEW DRUGS

The dependent variable (think of it as the effect) in my analysis is the percentage reduction in life-years lost before age 75 between 1970 and 1991. The independent variable (think cause) is the fraction of drugs pre-

scribed in 1991 that were approved in 1970 or later. I hypothesize that the greater the percentage of drugs prescribed in 1991 that were not yet available in the baseline year (1970), the greater the reduction in mortality.

Although there is only one explicit independent variable, the model does not assume that pharmaceutical innovation is the only source of mortality reduction. Changes in mortality are likely to depend upon a variety of factors, including changes in wealth, environmental quality and the prevalence of smoking. Note, however, that if the changes in these other factors did not vary from disease to disease, their effect would be captured by the constant term in the hypothesized algebraic relationship. Thus, my estimates of the effect of pharmaceutical innovation on mortality reduction depend entirely on diseases’ deviations from sample averages.

It is likely that changes in these other factors do vary to some extent from disease to disease. But there is no apparent reason to expect changes in most determinants of mor-

tality other than drug innovation to be correlated across diseases with drug innovation. It is not obvious, for example, why diseases for which many new drugs were developed should be the ones whose sufferers reduced smoking the most or whose wealth increased the most.

Ideally, one might estimate an expanded version of the model that includes a large number of other possible determinants of mortality change. But many of these are difficult to measure at the disease level. There are, however, several potentially relevant factors that we can measure, and will include in a more elaborate model of mortality reduction to check the sensitivity of our estimates to the inclusion of other real world factors in the analysis. They are: (1) the probability that the physician provides non-medical therapy – primarily counseling and education – to the patient, (2) the availability of a vaccine for the disease, and (3) the rate of introduction of new surgical procedures.

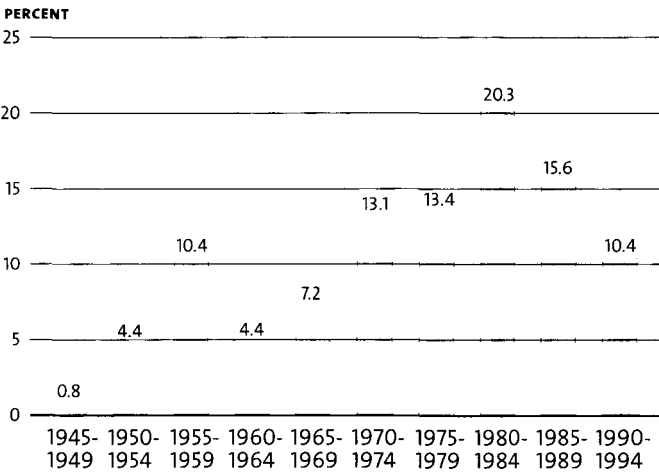
Estimates of the number of drugs prescribed in years following their approval by the FDA were obtained by combining data from several sources. The National Ambulatory Medical Care Survey (NAMCS) contains records from some 46,000 visits to doctors' offices in 1980 and 34,000 visits in 1991. To calculate the fraction of drugs that were approved by the FDA after a specific date, I linked the NAMCS records to the list of all new applications for drug approval. Almost half of the drugs prescribed in 1994 were approved after 1979; about a quarter were approved after 1984.

The FDA classifies new drugs as priority-review drugs, which represent an advance

over available therapy, and standard-review drugs, which have therapeutic qualities similar to those of drugs on the market. The FDA's goal is to act on applications for priority drugs within six months, and to make decisions on standard drugs within one year. All AIDS drugs are classified as priority drugs.

One might expect that new priority drugs, on average, have a larger impact on mortality than new standard drugs. I tested this hypothesis by estimating versions of the model in

**DISTRIBUTION OF DRUGS PRESCRIBED IN 1994,
BY FDA APPROVAL PERIOD**



which the new drug share is broken into two components: the shares of new priority drugs and new standard drugs in total drugs prescribed at the end of the period.

Of course, new drugs may confer benefits to patients other than mortality reduction. Elsewhere, I have investigated the effect of pharmaceutical innovation on morbidity and quality of life. Note that, if new drugs do indeed reduce mortality, one should examine the impact of pharmaceutical innovation on illness reduction, controlling for mortality reduction, since new drugs are likely to keep less-healthy people alive.

LONGER LIVING

I had mortality data for 1970, 1980 and 1991, along with data on the “vintage” distribution of drugs prescribed in both 1980 and 1991. So I estimated the model for the entire 21-year period 1970-91 and for the two sub-periods, 1970-80 and 1980-91. Since some

the largest new-drug class in 1980 – is 48, while the average age of patients receiving cardiovascular-renal drugs – the largest new drug class in 1991 – is 66.

By no coincidence, the average age of patients receiving any new drug in 1980 was 44, while the average age in 1991 was 52. Since

the clientele for drugs introduced in the 1980s tended to be older than the clientele for drugs introduced in the 1970s, one would expect the mortality reductions in the 1980s to be more concentrated among older patients. I tested this prediction by estimating the model for different categories of diseases, classified by the mean age at which people die from the disease.

Two disease classes – malignant neoplasm (cancer) of lymphatic and hematopoietic tissue, and pneumonia and influenza –

illustrated here exhibited very different patterns of mortality reduction and new-drug utilization during the 1970-91 period. Only one of the top five drugs prescribed in 1991 for the cancer class was approved after 1970, and the decline in per capita life-years lost (28 percent) was below the average for all diseases (43 percent). In contrast, all of the top five drugs prescribed to patients diagnosed with pneumonia and influenza were new drugs, and the decline in per capita life-years lost (74 percent) was well above average. The data for these two disease classes are thus consistent with the hypothesis that new drugs reduce mortality. But we need to analyze data on the full cross-section of diseases to test the theory in a disciplined way.



drugs must be consumed for a sustained period for their full health benefits to be realized, it would not be surprising if the longer-term estimated relationship were stronger than either of the two shorter-term relationships.

Moreover, the data indicate that the important new drugs introduced in the 1970s and the 1980s, as measured by sales, were aimed at different diseases and patients. Cardiovascular-renal drugs accounted for over a third of the new drugs prescribed in 1991, more than four times their share of new drugs in 1980; the new-drug share of hormones also increased sharply. By the same token, the average age of patients receiving drugs varies significantly across drug classes. The average age of patients receiving drugs used for pain –

HARD NUMBERS

The estimates show a highly significant positive relationship between the new drug share and mortality reduction in all three periods. The magnitude and statistical significance of the effect is larger over the entire 21-year period than it is in either of the two sub-periods. This is consistent with the idea that the long-run effects of new drugs on mortality are larger than the short-run effects. More than 40 percent of the variation across diseases in the 1970-91 reduction in mortality is explained by the new drug share.

An alternative way of analyzing this relationship is to group diseases into a number of categories on the basis of the new drug share, and then calculate the average reduction in mortality for each group of diseases.

CONTROLLING FOR OTHER FACTORS

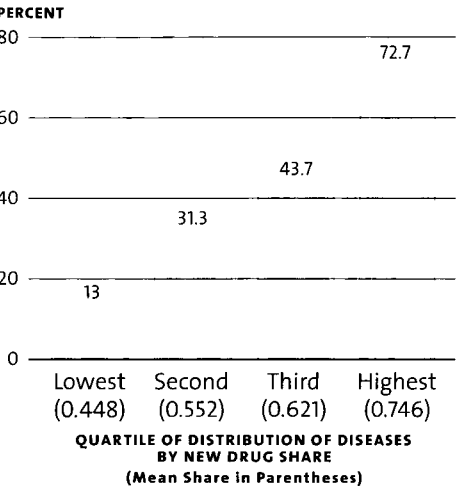
As noted earlier, the estimated effects of pharmaceutical innovation could be biased by the failure to control for other factors affecting mortality reduction. For example, educating patients about lifestyle is a potentially important source of mortality reduction. I controlled for the effect of improved patient knowledge by including the fraction of 1991 patients receiving other therapeutic services as an independent variable.

Likewise, vaccines, as well as drugs, contribute to mortality reduction. To control for the effect of vaccine availability on mortality reduction (in an admittedly imperfect way), I included a variable equal to 1 for diseases where a vaccine was available in 1991, and equal to 0 for where one was not. Including measures of counseling and education and of vaccine availability had very little effect on the estimated impact of pharmaceutical innovation on mortality reduction.

The third potential non-pharmaceutical source of mortality reduction is the rate of

introduction of new surgical procedures. Using data from the 1980 and 1991 National Hospital Discharge Surveys, I constructed an index, by disease, of the rate at which new surgical procedures were introduced during the period 1980-91. Unfortunately, it does not

MEAN 1970-91 REDUCTION IN LIFE-YEARS LOST BY DISEASES GROUPED BY NEW DRUG SHARE



appear to be feasible to measure the fraction of surgical procedures performed that are new, analogous to the fraction of drugs prescribed that are new, since comprehensive information on the date of introduction of all surgical procedures is not collected by the FDA. In any event, there is no statistically significant relationship between the surgery-innovation variable and mortality reduction for the 1980-91 period. Moreover, adding the surgery innovation variable to the equation has no effect on the estimate of the impact of pharmaceutical innovation.

SOCIETY'S RETURN ON DRUG INNOVATION

On average, each new drug approved during the period 1970-91 saved 11,200 life-years in

LONGER LIVING

1991 – and presumably will do so in all future years. So, by attaching costs to new drug approvals and economic value to life-years, we can calculate the social rate of return to investment in pharmaceutical innovation. Stewart Myers and Christopher Howe estimate the cost of a new drug approval to be \$697 million. David Cutler et al use a bench-

FIVE DRUGS MOST FREQUENTLY PRESCRIBED IN 1991 TO PATIENTS WITH TWO DIFFERENT DIAGNOSES

DRUG	PERCENT OF TOTAL PRESCRIPTIONS IN 1991	FDA APPROVAL DATE		DRUG STATUS	DRUG CLASS
		THROUGH 1970	AFTER 1970		
DIAGNOSIS: Pneumonia and influenza (ICD9 code 48) (74% reduction in per capita life-years lost, 1970-91)					
Amoxicillin	13.34%	1/18/74	•	Priority	Antibacterial
Albuterol	10.35	5/1/81	•	Priority	Bronchodilator
Ibuprofen	6.75	9/19/74	•	Priority	Anti-inflammatory
Cefaclor	6.13	4/4/79	•	Standard	Antibacterial
Ceftriaxone	5.34	12/21/84	•	Priority	Antibacterial
DIAGNOSIS: Malignant neoplasm of lymphatic and hematopoietic tissue (ICD9 code 20) (28% reduction in per capita life-years lost, 1970-91)					
Cyclophosphamide	8.16	• 11/16/59		Priority	Antineoplastic
Prednisone	7.66	• 9/15/55		Priority	Glucocorticoid
Vincristine	5.65	• 3/7/84	•	Priority	Antineoplastic
Digoxin	5.13	• 11/16/54		Priority	Cardiotonic
Allopurinol	4.7	• 8/19/66		Priority	Xanthine oxidase inhibitor

mark estimate of the value of a life-year of \$25,000. The aggregate value of 11,200 life-years, at \$25,000 per year, is \$280 million. The annual social rate of return to pharmaceutical innovation is thus \$280 million divided by \$697 million, or 40 percent – a remarkable figure.

This is a very rough estimate. On the one hand, the cost side of the estimate does not include government investments in R&D used by drugmakers. On the other, pharmaceutical innovation confers benefits beyond reduced mortality, like reduced hospitalization and surgical expenditures, reduced workdays and schooldays lost, and improved quality of life.

Previous investigators have argued that increased longevity is an important component of economic growth. And my estimates suggest that pharmaceutical innovation has contributed heavily to gains in life expectancy. More than 45 percent of the variation across diseases in the 1970-91 reduction in mortality can be attributed to the introduction of drugs. The average percentage reduction in life-years lost for the 19 diseases with the highest relative utilization of new drugs was over five times as great as the average percentage reduction in life-years lost for the 19 diseases with the lowest relative utilization of new drugs.

Stepping back, these are simply remarkable numbers. There seems little doubt that innovation in pharmaceuticals has been spectacularly valuable to society.

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THE King IS Dead

In 1948, the world of electronics was shaken, but not stirred, by the invention of the transistor at Bell Laboratories. Hardly anyone noticed, including AT&T, then the parent of Bell Labs. Four years later, Akio Morita visited the United States and saw in this small, crudely made electronic component the potential for a whole new world of radio. He went back to Japan and formed Sony. In the United States, calmer minds pondered the future of the transistor, laying out a supremely rational approach to developing this product gradually for specialty niches.



The king of electronic components at the time was RCA, followed by Sylvania and General Electric. It was clear that their dominance of the business – which was then mainly vacuum tubes – would give them the scale, the technology and the marketing wherewithal to control the fledgling transistor business. Within 20 years, however, none of these players was even ranked among the leaders in the industry, which was now the great-grandchild of the transistor business and dominated by producers of dynamic random access memories and microprocessors – Texas Instruments, Fairchild and

Long Live THE King!



Reading the Future of Drug Development in the Story of the Electronics Industry

Richard N. Foster

National Semiconductor. Twenty years after that, the industry had again gone through a major technological transition, to microprocessors, and this time Texas Instruments and Fairchild had been replaced by Intel and Mitsubishi, while Texas Instruments slipped from first to third. In short, companies that did not exist in the 1950s dominated the industry. The rout had been reasonably swift and utterly complete.

THE FUTURE OF DRUG DEVELOPMENT

Are we at the same point in drug development? Will competitors unknown today dominate the business two decades down the road?

That is a distinct possibility, and in concert with the history of the competitive shifts in markets that come as a result of fundamental technological change. These shifts are not unknown in the pharmaceutical industry. Of

the top 26 companies in 1980, just 10 survive as stand-alone enterprises.

The simple message from the semiconductor industry is that leaders lose because the burden of managing “legacy” assets drains financial and managerial resources from what it takes to remain competitive. Incumbents must compete with dozens of start-ups – none of which have a substantial chance of success, but collectively are almost certain to generate big winners from high-risk gambles on new technology. In addition, there has been enormous pressure for consolidation in the pharmaceutical industry. These two forces could be creating conditions for considerable change in market leadership over the next decade or two.

ELECTRONIC COMPONENTS AS HISTORY LESSON

The history of changes in leadership in electronics components parallels the change from vacuum tubes to silicon semiconductors. Sony became one of the first customers for the transistors to make small (for

their time) portable radios. Other applications soon followed. There was competition from germanium, another material with semiconducting properties, but silicon was more versatile and less expensive.

The Early Years

The early leaders in the transistor business were Transitron, Hughes and Philco, although the incumbents, Sylvania, GE and RCA, held

major positions. The U.S. Department of Defense quickly became both a major customer and a supporter of research in the field, leading to new technologies that allowed the integration of several transistors into a functional device. These small-scale devices found their way into phonograph players (yes, phonographs!), radios and even crude computers.

It was not long, however, before small-scale integration gave way to large-scale integrated circuits, and later to a very large number of transistors on a single chip (VLSI). The technology mostly served the end of providing electronic memory that could be interrogated to find any bit of data, no matter where it was stored, in real time. Called dynamic random access memories (or DRAMs), the components dominated the business for its first three decades.

Most of the intermediate steps between small scale integration and VLSI brought new industry leaders. And throughout this period, investors were richly rewarded; the semiconductor industry significantly outperformed the capital markets from 1955-85.

Then the Deluge

But in 1984, DRAM prices collapsed. The industry was now attracting entrants from all over the world – notably from Japan. And in 1983-84, four major Japanese companies (Fujitsu, Toshiba, NEC and Hitachi) announced their intention to build global-scale semiconductor plants. When added to the current world supply of semiconductors, those plants’ output would leave the world awash in semiconductors.

The Japanese claimed they were in the business for the long haul, and thus willing to bear short-term losses. They were intent on riding market share and Moore’s Law (computer speed will double every 18 months) to cost and performance dominance. That laudable

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purpose delighted electronic-device makers, who were busy designing products that took advantage of ever-cheaper memory. The market continued to expand rapidly, but margins became ever thinner and the market value of the industry tumbled.

What was missed by the industry and investors alike was a perverse corollary to Moore's Law: the cost of plants to produce transistors at efficient scale was increasing almost as fast as the power of the chips. Today, a semiconductor plant costs billions of dollars, limiting the industry to players with enormous capital resources. Thus began the great rout of 1984, which wiped out every undercapitalized producer.

New Day = New Leaders

The industry got back on its feet in the late 1980s. This time, the energizer was not the DRAM, but the microprocessor. And that brought a new industry leader, Intel, to the fore. Semiconductor processing technology had advanced far enough by the mid-1980s to allow engineers to build a whole computer on a chip. Intel exploited this advance, while virtually exiting the DRAM business that had been its mainstay. Indeed, Intel's willingness to jettison its legacy assets was one of the most courageous decisions made in American business in the past quarter-century, and is still a model for other companies coping with a tsunami of technological change.

Lessons Learned

How to generalize from the semiconductor case? Try these six lessons:

1. Incumbents as defenders of the current

DICK FOSTER is a director of McKinsey & Company, and the co-author of *Creative Destruction: Why Companies That are Built to Last Underperform the Market*.

order are more vulnerable than conventional wisdom would lead them to believe. No individual attacker has an advantage; only a few will survive. But as a class, the attackers will win if they have a strong potential value or cost proposition.

2. Straight-line extrapolation of past performance is never an adequate basis to forecast future performance. Performance is a result of the collective economic forces in the industry. High profits attract competitors – too many competitors – who then oversupply the market and are often extinguished by these collective forces. While it is tempting to look at individual companies to understand an industry, in the end the only thing that counts are the broader forces driving supply and demand.

3. Few companies can ride the wave from one technology to another. Attackers quickly become defenders, and are vanquished by new attackers as they fall prey to the very strategies they used to achieve their initial successes. Skills and culture are necessary for success, but are not sufficient to overcome the difficulty of caring for legacy assets and fending off new competitors financed by risk-prone investors.

4. Capital markets make mistakes. Far from being short-term oriented, the capital markets are very long-term oriented. And long-term forecasting is very hard in dynamic industries that can grow quickly, top out, and restart in a different direction.

The capital markets most often err as industries move through inflection points. If the growth of an industry is about to accelerate, price-to-earnings multiples are likely to be lower than is appropriate. This has been the case in the drug industry over the past two decades. Conversely, when a period of slowing growth is approaching, markets often overvalue the industry. Mistakes in long-term

forecasts, often made near inflection points, can result in excess returns for considerable time (as in the semiconductor industry) followed by crashes and then Phoenix-like rises. There is nothing harder than managing a business that is working hard, doing the right things and producing growing earnings, all while the stock price is collapsing. Yet this happens repeatedly in high-technology industries – it comes with the territory.

Intel's willingness to jettison its legacy assets was one of the most courageous decisions made in American business in the past quarter-century.

5. The battles between attackers and defenders are often protracted. The rate of play is determined by the relative rate of cost reduction (or price reduction in the marketplace) coupled with the strength of balance sheets. If relative costs are approaching one another slowly and balance sheets are strong, defenders can fight for years. But when costs are coming down quickly and balance sheets are weak – as they often are in biotechnology companies – noble battles can be lost quickly. In the battle between pharmaceutical makers and biotech enterprises, the pharmas will have the advantage of deeper pockets. Woe unto biotechnology companies that do not act accordingly.

That said, the collective balance sheet of the whole biotechnology industry will support repeated attacks without losing much innovative momentum, and woe unto the pharma that does not recognize this. Even though pharmaceutical margins are much higher than semiconductor margins, balance sheets can still be stressed — as, for example, Schering-Plough has discovered over the past two years. It is not about earnings or long-

term potential. It is about cash – both current and future – and always has been.

6. Probably 1 out of 10 of the original semiconductor companies with deep pockets have made it, and the consolidation is not over. Numbers like these will almost certainly be repeated in biotech. Not all those semiconductor companies that disappeared suffered painful deaths. Many were absorbed by competitors, which themselves may not have

made it. In the end, buy-and-hold investors, those with the stock of major manufacturers, witnessed the end of their exceptional returns, and often saw an absolute decline in wealth.

WILL A TRANSITION COME IN PHARMA/BIO TECHNOLOGY?

All these lessons are relevant to pharma/biotechnology. If the transition unfolds in a way parallel to the semiconductor industry, giants will fall, new companies will emerge, fortunes will be made and lost, investors will get rich and lose everything, and new regulations will emerge to correct the problems.

There are Important Differences...

Unlike semiconductors, pharma/biotechnology is not supported by the Defense Department. Indeed, pharma/biotechnology companies are regulated, and even compete for knowledge resources with government health agencies.

In addition, patents offer less protection in the semiconductor industry than in pharma/biotechnology. And as history suggests, this

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should slow change. Pharma has had a much lower, and more stable, rate of company formation than almost any other industry in the United States. In fact, pharma's investors' returns have supplanted the semiconductor industry as the most rewarding returns over the past 20 years.

This performance has been based on a spectacular record of innovation. In the past 10 to 15 years, the industry has developed a startling array of products (see page 33).

Biotechnology companies have also made significant advances, including white-blood-cell stimulants like erythropoietin (Epogen and Nupogen). There are now almost 500 biologicals in the Food and Drug Administration's clinical process, equaling about one fifth of the number of pharmaceutical products under development.

But successes are not inevitable. Pharma suffered a collapse in stock performance in the mid 1970s, very much like the one experienced by semiconductors in 1984. Hardly anyone remembers that now, but after years of doing well compared to the markets, investors were blindsided. It could happen again.

... But Similarities as Well

The biotechnology industry, however, does not share the characteristics of pharma. Unlike drug makers, biotech has experienced an exceptionally high rate of company formation. And while this pace is slowing, biotechnology is still on a much faster track than pharma. In this sense, the biotechnology industry looks more like semiconductors than pharmaceuticals. During this period, some significant biotechnology companies have emerged, including Amgen, Genentech, and Chiron. But it is still very early to extrapolate trends. Strong early competitors also emerged in semiconductors. But as the key technolo-

gies changed in that industry, competitive leadership changed as well.

Another similarity between biotech and semiconductors is the extraordinary technological potential remaining to be exploited. Knowledge of the human genome is only a few years old. Moreover, only a few dozen species have been analyzed. Analysis of others is essential for full understanding of what is normal in the human genome. This knowledge will come; it is virtually guaranteed at this point. Cellular signaling pathways are just beginning to be reverse-engineered. This is a tricky, multidisciplinary science, but it is being addressed.

Moreover, all this science is being put in the service of drug innovation. Gleevec, developed by Novartis, may be the model for a series of biologically informed cancer-drug development processes. For the first time, the potential for rapidly cycling between biological and chemical insight in the name of developing ever-more-effective, lower-risk, small-molecule drugs is fully practical. Not every company is able to do it. Changing from rational drug design to rapid cycling design requires a change in organizational culture. That was true for semiconductors as well. The essential nature of the chip-design process changed, enabling more technological barriers to be hurdled, costs to decline and development cycles to be accelerated.

Drug development is not the only prize here. Genetic screening may be very helpful for spotting potential Type II diabetics, thus allowing relatively simple diet changes for such people to help stave off that degenerative disease.

Finally, we can count on the capital markets to be just as inept in forecasting the future of pharma/biotech as they were in forecasting the future of semiconductors. As noted above, pharma has one structure and

the biotechnology industry has another. The pharma structure is quite robust and difficult to change. The biotechnology structure is more flexible, more innovative and more like the semiconductor industry.

Accordingly, the competition between pharma and biotechnology is quite different from the battle between generations of the semiconductor industry. Not only will the traditional competition seen in semiconductors be present in pharma/biotech, there will also be a new feature to this battle – the conflict between industry structures. The outcomes of battles on new turf are particularly difficult to forecast.

The uncertainty here is already apparent as we come out of a recession and market collapse. The eagerly awaited biotech window opened briefly on Wall Street, but so far it has crushed the fingers of those who chose to reach through. If the doleful mood among investors is replaced by euphoria, we will be setting up the next disappointing cycle.

WHAT DOES THIS MEAN FOR BIOTECHNOLOGY COMPANIES, PHARMAS AND INVESTORS?

It does not take a clairvoyant to imagine more effective drugs with fewer side effects. But getting from here to there will be a hard slog. New products will burst onto the scene, only to be replaced by more effective ones well before patents expire. Of course, patients will benefit from the competitive innovation. But biotechnology companies, pharmas and investors may be burned in the struggle.

For Biotechnology Companies

For the biotechnology companies, the messages are clear. Maintain a strong balance sheet – cash to finance multiple years of heavy losses would be good. And build a diversified product portfolio – the probability of several

Drugs developed in the past 15 years

- **Anti-ulcerants**
(Zantac and Prilosec)
- **Cholesterol-lowering agents**
(Zocor and Lipitor)
- **Recombinant insulin**
(Humalin and Novolin)
- **Combination antiretroviral therapies**
(Virocept and Retrovir)
- **Selective serotonin reuptake inhibitors** (Prozac and Zoloft)
- **Atypical antipsychotics**
(Zyprexa and Risperdal)
- **Third-generation antibiotics**
(Levaquin and Zithromax)
- **Novel targeted cancer therapies**
(Herceptin and Gleevec)
- **Better transplant-facilitating drugs**
(Sandimmune)

new drug initiatives failing is far less than the probability than any one drug will fail. Last, biotech companies should be conscious of the rate at which they begin to build legacy assets that will entrap them later on.

For Pharmas

The challenge will be the same as that faced decades ago by vacuum-tube manufacturers. That knowledge, however, can hardly be comforting. Some analysts will argue that the intellectual property protection afforded pharmas will save them. But the market power of the pharmas is weaker today than in the recent past. Hundreds of biotech start-ups in the United States alone are ready to take a shot at toppling incumbents. And some of them have both strong balance sheets and robust portfolios. Some biotechnology companies will undoubtedly develop products

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that make it in the marketplace. They will be rewarded with sky-high price-earnings ratios, which will give them the leverage to finance the next set of challenges to pharma. And so it will go.

The test for senior managers of pharmas will be to use the market, rather than any single company or group of peers, as a standard of performance. It is the competition from the periphery that counts, not the activity of the core. It is the products and companies that succeed, not those that fail.

For Investors

For investors, the next 10 to 15 years promise an exciting ride. Biotechnology is not semiconductors or computers or software or telecoms, each of which is beguilingly understandable by comparison. Biotechnology is complex beyond imagination. To be sure, specialized venture-capital firms are supporting this industry with capital and expertise. But there has been a backlash among the biotechnology entrepreneurs, who often feel that venture capital is too expensive. Increasingly, private money is being raised without VC help.

Limited partnerships are looking for ways to simplify investing in this complex area. Thus, some investors are finessing the problem by investing in companies where “Dr. X” who is “the most distinguished ‘Y’ologist in the world” sits on the scientific advisory board. Others are reverting to the buddy system – as in “Investor Z made a lot of money in software, so I am sure he knows where the best biotechnology investments are.”

Neither approach will work. There will be no substitute for understanding the basic science, the risks that come with it, the need for a balanced portfolio, the highest ethical standards and a strong balance sheet. Biotechnology will not be for everyone, but eventually

everyone will want to become a biotechnology investor. That will be the time to have your money in bank CDs!

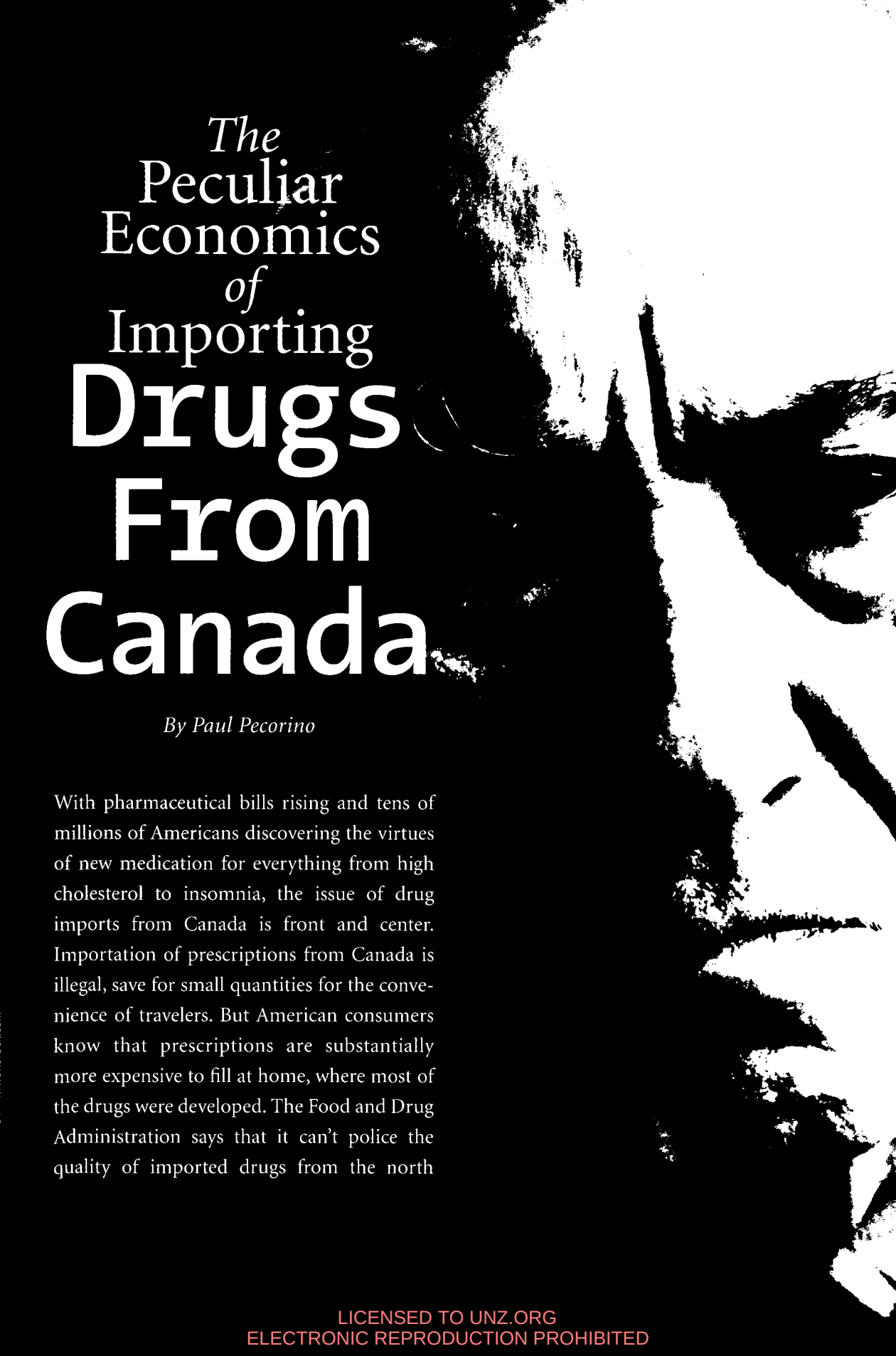
Innovation will continue in medical devices, test equipment, monitoring and a variety of other health-related fields. But there is no business with both the attractions and the risks of pharma/biotechnology. A great deal of value will be created here. We shall see if today’s major pharma companies have more skill than the leading electronic-component companies had a half-century ago. History suggests they won’t.

The experience of one other industry, born as the nation came out of the recession of 1973 and 1974, is relevant. Consumers took the country into that recession and then brought us out – but not by patronizing old-style retailers. New-format stores – The Limited, Gap, Home Depot, Wal-Mart – burst through. Those savvy, or lucky, enough to have invested \$10,000 in The Limited in 1974 and then hold on until the heady days of 1989 would have ended up with \$4.5 million. It is not unreasonable to expect a few new biotechnology companies to strike it rich this way, as well.

At the end of the 19th century, the social commentator G.K. Chesterton wrote:

The real trouble with this world of ours is not that it is an unreasonable world, or even that it is a reasonable one. The commonest kind of trouble is that the world is nearly reasonable, but not quite. Life is not an illogicality; yet it is a trap for logicians. It looks just a little more mathematical and regular than it is; its exactitude is obvious, but its inexactitude is hidden; its wildness lies in wait.

The pharma/biotechnology transition will prove this true once again. Medicine is autocatalytic – good medicine begets more good medicine. The king will die. Long live the king. 



The Peculiar Economics *of* Importing Drugs From Canada

By Paul Pecorino

With pharmaceutical bills rising and tens of millions of Americans discovering the virtues of new medication for everything from high cholesterol to insomnia, the issue of drug imports from Canada is front and center. Importation of prescriptions from Canada is illegal, save for small quantities for the convenience of travelers. But American consumers know that prescriptions are substantially more expensive to fill at home, where most of the drugs were developed. The Food and Drug Administration says that it can't police the quality of imported drugs from the north

DRUGS FROM CANADA

land, while economists argue that free trade in pharmaceuticals would, ironically, bring with it Canada's system of drug price controls. To further complicate matters, John R. Graham of the Fraser Institute, a market-oriented think tank based in Vancouver, argues that at least part of the price difference is driven by intentional – and benign – price discrimination by drug companies rather than by the heavy hand of regulation.

How should we think about the issue? First, it is plainly not a classic dispute about free trade pitting the interests of consumers against those of inefficient domestic sellers. After all, the importation of prescription drugs from Canada is taking place against the wishes of the manufacturers of the drugs. And the standard economic nostrums simply don't apply.

Second, there is the thorny question of how well the incentives of U.S. drug makers mesh with the public interest. On the one hand, the owners of drug patents are monopolists in the sense that they have incentives to keep prices far above the incremental cost of production. On the other, the prospect of earning high profits tends to speed the pace of innovation – which, in the case of lifesaving drugs, is very much in the public interest.

For the sake of argument, I assume that public and private incentives are sufficiently well aligned that any significant drop in drug company profitability would, on balance, harm consumers as well as drug company stockholders. Thus, I focus more on the profits of United States drug companies than on the direct benefits to American consumers that might result from Canadian drug imports.

PAUL PECORINO teaches in the department of economics, finance and legal studies at the University of Alabama.

CANADIAN PRICE CONTROLS

In Canada, the Patented Medicine Prices Review Board sets a maximum wholesale price for new drugs and regulates the rate at which prices may increase for existing drugs. While economists generally dislike price controls because they undermine efficiency-enhancing incentives, it is important to realize that such controls on drugs may still serve the parochial interests of Canadians.

When a country faces a foreign monopoly (as is the case for every drug whose patent is held by a foreign manufacturer), price controls create a countervailing market power that lowers the cost of imported drugs without reducing their availability. Of course, Canadian price controls will affect the incentives to innovate among Canadian drug companies. However, the impact is likely to be negligible because Canadian companies are minor players in worldwide drug development and because prices of Canadian drugs sold in the United States would not be subject to controls. Thus, one key factor in understanding the re-import issue is understanding that price controls allow Canadian consumers to “free ride” off the research and development investments of United States pharmaceutical companies.

Here I have analyzed the implications of allowing drug re-imports from Canada. Note that classical supply and demand analysis isn't much use since there is effectively only one Canadian buyer – the government. The theory of games, in which outcomes are determined through bargaining, does apply, however. To this end, I employ a widely used device known as a Nash bargaining game (named after John Nash, who won a Nobel Memorial Prize in Economic Science for pioneering the approach).

The outcome of a Nash bargaining game depends upon two features, the first of which



When a country faces a foreign monopoly, price controls create a countervailing market power that lowers the cost of imported drugs without reducing their availability.

is the relative bargaining power of the two parties. The Canadian government obtains higher benefits when the controlled price is lower, since this means lower costs for Canadian consumers. The drug company, by the same token, obtains greater benefits from a higher price. A higher price raises profits as long as it does not exceed the price a monopolist would charge in a classic market in which consumers could not bargain. The Nash bargaining approach is flexible enough to allow the bargaining power for Canada to range anywhere from 0 (all the power lies with the U.S. company) to 1 (all the power lies with Canada).

The outcome also depends upon the “threat point” of each party. The threat point reflects how well each party does in the event

of a bargaining failure. If negotiations break down and there are no Canadian sales of the drug, the Canadian government receives zero benefit, reflecting the fact that its consumers are denied the use of the drug. The U.S.-based drug company receives no profit on Canadian sales, but still receives the monopoly profit on sales in the U.S. market. This is another key element to the analysis: no stance by the Canadian government can rationally lead a U.S. drug company to accept a profit outcome that is worse than it would receive from selling in its home market alone.

The economic surplus received by the U.S. drug company in the bargaining game is the sum of its profits from sales in Canada and the United States, less the monopoly profits it would earn in the United States in the event

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of a breakdown in negotiations. When re-imports from Canada are not allowed, there is perfect market segmentation. A price is negotiated in Canada – but this price has no ramifications for the U.S. market, where the seller remains free to charge the monopoly price.

In versions of the model where drug re-imports are allowed, I make the extreme assumption that the negotiated price in Canada becomes the U.S. price – that is, U.S. consumers buy nothing unless drug sellers match the Canadian price. This reflects the concerns of some critics that, under the re-importation regime, the United States will effectively import Canadian price controls along with the drugs. It also reflects a standard assumption in trade theory that, in the absence of barriers to trade, one price will prevail in all markets.

The assumption that the controlled price negotiated in Canada becomes the United States price if re-importation is permitted has important ramifications for the outcome of the Nash bargaining game. There are several ways to conceptualize what happens, but the easiest may be to think about the cost of a price concession to the United States drug company. Compared with the no re-import regime, the cost of price concessions to the Canadians is high because the concessions not only lower profit margins in Canada, but also lower profit margins in the much larger U.S. market. Hence, it should not be surprising that the model predicts that a drug company will make fewer price concessions when both national markets are affected. This prediction matches the common sense observations of analysts who have argued that re-imports will lead to substantially higher prices in Canada.

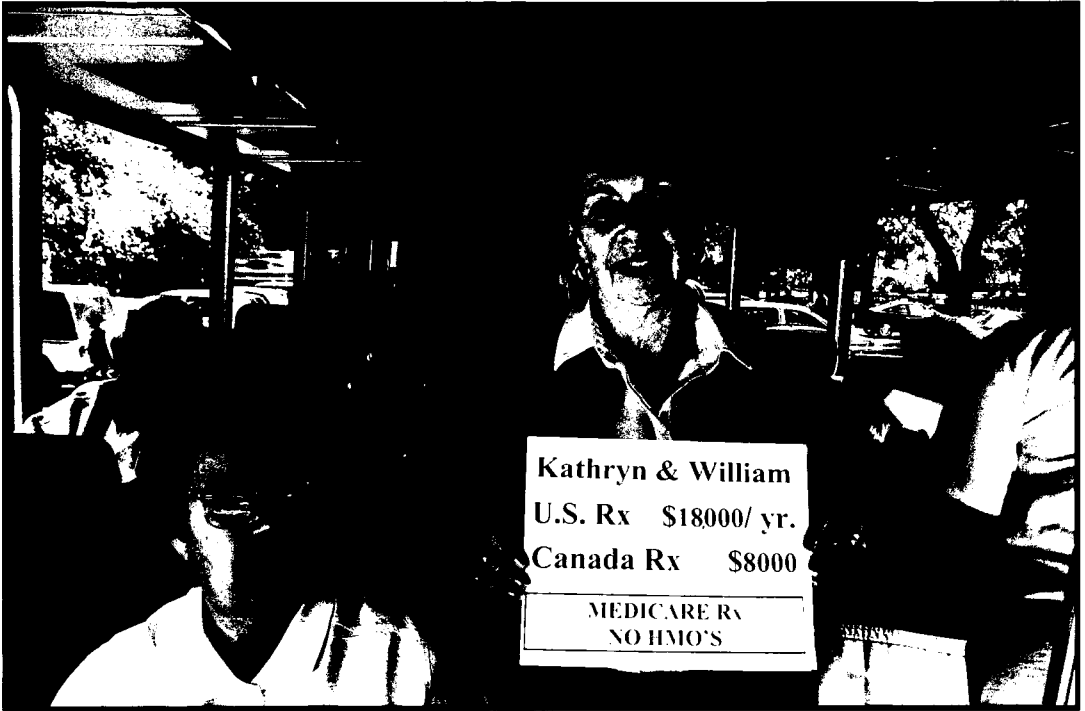
While the Canadian price rises as a consequence of permitting re-imports, the price in

the United States tends to fall. Thus in the re-importation scenario, profit margins rise on Canadian sales as they fall on United States sales. Note the ambiguity here: the net impact on total drug company profits can't be determined without more information about the demand for drugs in Canada.

However, some specific assumptions about demand do lead to striking conclusions. If Canadian demand is linear – if the demand curve is approximately a straight line – drug company profits are always higher when re-imports are allowed than when they are barred. That is, the gain from the higher Canadian prices negotiated by the drug company always more than offsets the losses from the lower U.S. price. And this is true regardless of the bargaining power of the Canadian government. Put it another way: squeezing the drug maker by permitting drugs for the Canadian market to leak back into the American market gives the seller the backbone to face down the Canadian's attempts to negotiate lower prices.

Next, I experiment with a somewhat more complicated hypothetical Canadian demand curve, one with what economists call a “constant price elasticity.” If, for example, the price elasticity were 3, a 1 percent increase in price would always lead to a 3 percent decrease in demand. Here, it is not possible to derive outcomes from algebra alone, so I resort to simulations under which I make specific assumptions about the magnitude of key parameters – notably, the elasticity of demand and size of the Canadian market, and the bargaining power of the two sides.

The computation is more complicated, but the results are strikingly similar to the initial case: drug company profits are higher if re-imports are permitted. The increase in profits is always quite small, but these results suggest that allowing re-imports would not be disas-



trous for drug company profitability.

Is there a good reason to think that these two hypothetical cases represent the rule rather than the exception? When re-imports are not allowed, the drug company sets a price in the United States that exacts every last penny of profit from the United States market – the seller operates at the top of the metaphoric profit hill. And being at the top of a profit hill implies that a small change in price has essentially no effect on profits. Thus, a small price cut will cause a negligible reduction in company profits. By contrast, price controls imply that the Canadian price is not the same as the profit-maximizing price for Canada: the company is operating on the positively sloped portion of the profit hill. As a result, a small price rise can lead to a relatively large increase in company profits.

This does not seal the case because a move to a re-import regime would in fact cause a large change in prices in one or both markets, while the discussion above explicitly refers to

“small” price changes. Nevertheless, the underlying logic does help to explain how the rise in profits from Canadian sales can exceed the fall in profits from United States sales if re-imports are allowed.

If a world in which re-imports are permitted would be a more profitable world for drug makers, why does the industry fiercely oppose legal reform? One reason is history: if the old prices charged in the Canadian market cannot be renegotiated, the drug companies will see their profits tumble when the drugs surge back into the United States at the Canadian price. Rather than allow these previously negotiated prices to prevail in the United States, the drug companies would almost certainly restrict or suspend sales to the Canadian market.

Note, too, that if the drug companies attempted to force a renegotiation of existing prices or sharply restricted sales to Canada, there would be some danger of an extreme response by the Canadian government. For example, Canada could allow manufacturers



located in Canada to produce medicines protected by U.S. patents. This is an important caveat to the analysis above.

PRICE DISCRIMINATION

A crucial assumption to my bargaining model is that the demand for drugs in Canada is the same as the demand in the United States – only proportionally smaller because fewer people live in Canada. As a result, an unregulated profit-maximizing U.S. drug company would charge the same price in both markets. Or, to put it another way, there are no incentives for drug makers to segment the two markets the way, say, airlines discriminate between business travelers and vacationers willing to purchase their tickets far in advance.

This assumption reflects the widely held view that Canadians get better deals on drugs solely because of government price regulation. But John Graham notes that Canadians' incomes are well below those of their U.S. counterparts – and thus a large part of the price gap may reflect the desire of the drug companies to charge more to Americans because they are willing to pay more.

Among other things, this would explain why drug companies oppose re-imports: under this scenario, price discrimination between the two markets is necessary to maximize profits for the same reason that price discrimination among classes of air travelers is necessary to maximize airline profits (or, at least in the latter case, to minimize losses).

But even if Graham is wrong about the Canadian market, there plainly are markets in which drug companies would be better off if they could discriminate on prices. For example, drug makers would certainly choose to sell their products at much lower prices in poor countries, provided markets in rich countries could be walled off. There's no point in charging \$4 for a daily dose of anti-hypertension medicine (that costs only 40 cents to manufacture and distribute) in a country where hardly anyone earns more than \$10 a day.

It's also worth pointing out that this type of price discrimination is in everyone's interest. Any sensible re-import policy must acknowledge the compelling argument for making lifesaving drugs available in low-income countries. Thus, it would be foolish to implement a re-import policy that does not differentiate between, say, Canada and Chad.

For the sake of argument, assume that all of the price difference between the United States and Canada is caused by profit-maximizing discrimination on the part of the U.S. drug companies. Would Washington have a

Would Washington have a compelling interest in enforcing market segmentation between these two countries? Probably not.

compelling interest in enforcing market segmentation between these two countries? Probably not. While we would expect drug company profits to fall somewhat if the two markets were integrated, there would still be ample incentive for innovation in serving such a large and wealthy aggregate market. And in the absence of a compelling interest, it seems reasonable to give the benefit of a doubt to free markets.

However, a free-market approach would still allow drug companies to enforce contracts with their wholesalers that banned wholesalers from selling the drugs in another country. Since the wholesalers in question are Canadian, this would be a matter for Canadian civil courts to decide. Moreover, since price discrimination and the ban on re-imports both favor the interests of Canadian consumers, the Canadian government may yet wake up and help to enforce these contracts.

WHO'S ON FIRST?

If low Canadian drug prices are largely driven by Canadian price controls, allowing re-imports should lead U.S. drug companies to bargain harder in Canada and thereby drive up the Canadian price. However, even if drug profits generally fall as a result of re-imports, it is unlikely that the decline would be large.

At a minimum, drug companies will always make at least as much profit selling in the two markets as they would from selling in the much larger United States market alone. But in most instances we should expect them to do significantly better than this.

On the other hand, what looks like price

regulation with teeth may be little more than a wink and a nod; price differences may largely be the result of voluntary price discrimination in which the country that can afford to pay more (the United States) does pay more. In this case, a policy that undermines market segmentation by allowing re-imports will reduce drug company profits.

But it is hard to see why the United States government should go out of its way to fight re-importation if the only purpose is to support a policy of intentional price discrimination by U.S. companies.

While the economics of the problem suggests that, on balance, re-imports may be a good thing, it should be clear that the gains for American consumers would be much more modest than existing price differences with Canada suggest. Indeed, since the U.S. market is so large compared with Canada's, integration of the two markets is certain to lead to drug prices that are close to current U.S. prices.

Of course, small price reductions on millions of prescriptions for Lipitor, Fosamax and the like could add up to a lot of money. And since, in the price-control scenario, this would probably be combined with small increases in profits for the drug companies, a policy permitting re-imports is likely to benefit the United States at Canada's expense.

A re-importation policy could thus undo what is essentially an optimal Canadian trade policy, under which the Canadians benefit at the expense of the United States. Does anyone in Washington really understand what's going on here?

M



Malaria, tuberculosis and the strains of HIV common in Africa kill five million people each year, overwhelmingly in poor countries. Vaccines offer the best hope for conquering these diseases. Yet research on such vaccines remains minimal, largely because prospective developers fear that they will not be able to sell sufficient quantities to recoup their investments.

This under-investment reflects not only the concentration of these diseases in poor countries but also market distortions that limit research on treatments for these diseases – particularly on vaccines. Prices for vaccines for developing countries have historically been low because, once pharmaceutical companies have sunk investments in R&D to develop them, governments often use their powers as regulators, major purchasers and arbiters of intellectual property rights to keep prices down.

Research on vaccines is an international “public good;” hence none of the many countries that would benefit from a malaria, tuberculosis or HIV vaccine has sufficient incentive to encourage research by unilaterally offering to pay higher prices. Property

Making Vaccines Pay

Creating Incentives to Stop AIDS, Tuberculosis and Malaria

rights in pharmaceuticals have therefore historically been weak in poor countries. Most vaccines sold in those countries are priced at pennies per dose – a tiny fraction of their social value. More expensive on-patent vaccines have typically not been purchased by the poorest countries. Thus, private developers lack incentives to pursue research on diseases that primarily affect poor countries.

Programs to encourage development of new products can be classified in two broad categories: “push” programs, which subsidize research, and “pull” programs, which reward developers for actually producing the desired product. Government-directed

By Michael Kremer

MAKING VACCINES PAY

push programs have proved well suited for basic research. But for the later stages of research, the pull approach has important advantages.

With pull programs, the public pays only if a successful product is actually developed. This feature gives pharmaceutical firms and scientists strong incentives to select projects that they believe have a reasonable chance of leading to useful products and to focus on creating viable vaccines or drugs rather than pursuing other goals.

Moreover, pull programs can help to ensure that if new products are indeed devel-

no funds would be spent; if it succeeded, tens of millions of lives would be saved.

VACCINES AND HEALTH IN POOR COUNTRIES

Infectious and parasitic diseases account for one-third of the disease burden in low-income countries and nearly half of Africa's disease burden. In contrast, infectious and parasitic diseases account for only 3 percent of the burden in high-income countries. Burdens can be compared across countries using the concept of disability-adjusted life-years (DALYs), which takes into account not only the lives lost through disease but also the

Connecticut spends more on health than the 38 low-income countries of sub-Saharan Africa combined.

oped, they will reach those people who need them. For example, a pull program's sponsor might guarantee that for an effective malaria vaccine, it would pay the developer \$20 for each of the first 250 million people immunized, subject to a 10 percent co-payment by the recipient country or other donors.

A legally binding commitment to finance vaccines for poor countries could be implemented by international organizations like the World Bank, by national governments, by private foundations like the Bill & Melinda Gates Foundation, or by a combination of those groups.

If a vaccine commitment failed to stimulate the development of an effective vaccine,

number of years of disability caused.

Differences in environment contribute to this gap. Poor countries are generally in the tropics, and the high biodiversity of the tropics gives rise to more-numerous and more-virulent infectious diseases. They also have more effective disease vectors, like African mosquitoes that spread malaria. Poverty leads to poor nutrition, sanitation and education, all of which contribute to the spread of diseases. Dysfunctional or desperately poor governments fail to provide clean water, sanitation and public health programs like antituberculosis campaigns.

Another key reason for the spread of infection is the reality of weak health care systems in poor countries: budgets are low, government health care workers are vulnerable to corruption and the ranks of private health providers are filled with quacks, making it difficult to deliver all but the simplest health care. Low-income sub-Saharan African na-

MICHAEL KREMER is Gates professor of developing societies at Harvard University, a senior fellow at the Brookings Institution and a nonresident fellow at the Center for Global Development. The ideas in this article will be presented in greater detail in a book to be published by Princeton University Press in 2004.

tions spent only 6 percent of their average \$300 per capita GDP on health – around \$18 per person. Connecticut spends more on health than the 38 low-income countries of sub-Saharan Africa combined. Whereas the United States has 2.7 trained physicians per thousand people and Europe has 3.9, sub-Saharan Africa has only 0.1.

Still, health in developing countries has improved tremendously over the past 50 years, due largely to the adoption of cheap, easy-to-use technologies. Vaccines are the paradigmatic example. They do not require diagnosis for use, can be taken in a few doses instead of long-term regimens, and rarely have major side effects. Hence, compared to drugs, they can be delivered more easily by health care workers with limited training. Seventy-four percent of the world's children receive a standard package of cheap, off-patent vaccines through the World Health Organization's Expanded Program on Immunization, and these vaccines save 3 million lives per year at a cost of only pennies per dose. The vaccine-driven eradication of smallpox more than two decades ago averted 40 million deaths.

In contrast, despite dramatic price reductions, only 50,000 people in Africa are taking antiretroviral medicines for HIV/AIDS, while 25 million are estimated to the disease and 4.1 million have reached the stage of the disease where treatment would be considered appropriate.

Expenditures on vaccines save more lives for a given budget than almost any other health measure, largely because of the low cost of delivery. Thus, vaccines are the best hope for a long-run sustainable solution to the problem of infectious diseases in the developing world.

R&D AND POOR COUNTRIES

Very little R&D is done on vaccines or drugs oriented primarily to the developing world. Of the 1,233 drugs licensed worldwide between 1975 and 1997, only 13 were directed at tropical diseases. Of these, five came from veterinary research, two were modifica-



tions of existing medicines, and two were produced for the United States military. Only four were developed by pharmaceutical firms specifically for tropical diseases in humans.

In 1992, half of global health R&D was undertaken by private industry. But according to the World Health Organization, less than 5 percent of that was spent on diseases specific to poor countries.

While diseases like schistosomiasis and



While diseases like malaria are particularly starved of research funds, even HIV/AIDS research, which is more active, has not been oriented toward the needs of the countries where the disease is most prevalent.

malaria that almost exclusively affect low-income countries are particularly starved of research funds, even HIV/AIDS research, which is more active, has not been oriented toward the needs of the countries where the disease is most prevalent. Most research has been on drugs, rather than on vaccines. Most candidate vaccines for HIV tested worldwide are based on what researchers call clade B, the strain widespread in the United States, Eur-

ope, Australia and Latin America, rather than clade C, the most common strain in Africa, where two-thirds of new infections occur.

A possible reason that research on vaccines for malaria, tuberculosis and HIV is so limited, despite the pressing need, is that developing vaccines for each represents a formidable scientific challenge. Nonetheless, many scientists are optimistic. Recent advances in immunology, biochemistry and biotechnology have created tools for understanding the immune response to these diseases, as well as for testing the potential efficacy of candidate vaccines, both in the lab and in animals. Genetic sequencing of HIV and the organisms causing tuberculosis and malaria is either complete or advanced. This progress may help scientists create vaccines that aim at many different antigens, and thus will be more effective in the face of genetic diversity.

Thus, while the nature of the challenge may have slowed research, it is probably not the main reason for the disappointing pace of development. As noted above, there is an extraordinary divergence between the extent

of R&D devoted to rich-country and poor-country diseases. The more plausible explanation for the dearth of research on diseases of low-income countries is that their markets for advanced drugs are very small. Indeed, all of Africa constitutes just 1 percent of the global pharmaceuticals market.

Drug developers often do not even bother to take out patents in small, poor countries. Most of the key intellectual property underlying AIDS drugs is not patented in many African countries – presumably because the manufacturers did not consider protecting the local market worth the filing fee.

WHY MARKETS DON'T WORK FOR DEVELOPING-COUNTRY VACCINES

The small market for vaccines is due not only to low incomes in developing nations, but also to inefficiency in the markets for vaccines and in vaccine R&D. As a result, the rewards to a private developer would be far lower than the value people in poor countries would place on a vaccine, even given their low incomes. Thus, government aid aimed at vaccine research for neglected diseases would be highly cost-effective – even more so than aid for food, shelter and other desperately needed goods.

Economists often argue against aiming foreign aid at specific goods because, in most cases, recipients are the best judges of what they need most. If we were thinking only about goods like eggs, that would make sense. Where people place a high value on having more protein in their diet, they might spend their additional money on eggs. Farmers

would start raising more chickens and selling the eggs, thus supplying people with protein.

A key assumption driving this conclusion is that if people put a higher value on a product than it costs to produce, businesses will spring up to serve the need. However, that is not likely to happen with new pharmaceuticals. There are two critical differences between eggs and pharmaceuticals. First, people who buy eggs enjoy all the benefits themselves, while people who buy vaccines benefit

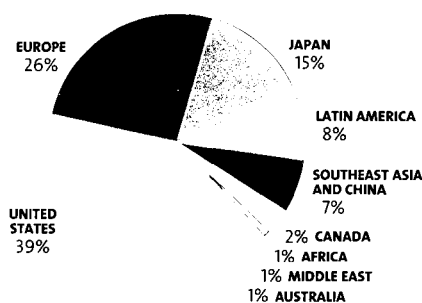
others by reducing the spread of disease. Second, the main cost of producing new pharmaceuticals is R&D. The key output of biotechnology and pharmaceutical firms is not a physical product, but knowledge, and it is hard for firms to capture the full ben-

efits. In particular, once invented, pharmaceuticals can usually be manufactured relatively cheaply, so firms that have not invested in R&D may end up as beneficiaries.

Vaccines may also be underproduced for other reasons. Consumers may be myopic in the sense that they are more willing to pay for treatment than for prevention. Many potential consumers in poor countries place limited credence in official pronouncements about vaccination benefits, and may wait to observe the effects on neighbors before getting vaccinations themselves. The chief beneficiaries of vaccines are often children, and some parents who make decisions on their children's behalf may not take their welfare into account in spending decisions.

All these factors suggest that the benefits

**WORLD PHARMACEUTICAL MARKET
SALES BY REGION (1998)**



Source: PhRMA Industry Profile 2000

MAKING VACCINES PAY

to society of R&D on vaccines are typically many times greater than the benefits that accrue to the developer. A malaria vaccine would produce social benefits conservatively valued at \$4 billion per year, while the total developing-country outlay for childhood vaccines is just \$200 million annually.

governments or by agencies like UNICEF, which use their market power as very large buyers to push down prices.

Governments have historically not paid vaccine developers anything near the societal value of vaccines for two main reasons. First, once pharmaceutical developers have made their R&D investments, governments have

A malaria vaccine would produce social benefits conservatively valued at \$4 billion per year, while the total developing-country outlay for childhood vaccines is just \$200 million annually.

Back-of-the-envelope calculations imply that a 20-fold gap between private and social value is likely. Thus pharmaceutical developers lack incentives to pursue research projects that would be worthwhile from the point of view of society as a whole. And by the same token, assistance from governments or non-profit agencies that encourages vaccine research potentially has a much higher payoff than other forms of economic or medical aid.

WHERE GOVERNMENT FITS IN

Patent protection can help developers to secure a greater portion of the benefits of R&D. But the monopoly associated with patents has a big downside: by allowing producers to charge far more than the incremental cost of manufacture, it prevents millions of people benefiting from products that are relatively cheap to produce at the margin. As a result, many poor countries have historically limited patent protection for pharmaceuticals. And, not surprisingly, drug companies have been reluctant to create products for their needs. This is particularly true for vaccines, which are nearly always purchased by

every incentive to force prices down to a level that covers only the manufacturing costs. This is true even if before developers have made their investment, the government sees the need to provide greater incentives (the time-inconsistency or sunk-cost problem). Second, because vaccine development is a global public good, each country has an incentive to free-ride off research financed elsewhere or induced by other countries' intellectual property protection. Each country benefits – but each prefers some other country to pay the costs of development.

The dearth of vaccine research for malaria, tuberculosis and variants of the HIV virus prevalent in Africa thus stems not only from abject poverty but also from free-rider problems that plague the production of all global public goods. Large countries like the United States know they risk stemming future research if they free-ride. But small, poor countries like Uganda know their policies barely affect research incentives.

The free-rider problem is particularly severe for countries that constitute only modest fractions of the world market for pharma-

ceuticals and reap proportionately small fractions of worldwide research benefits. For example, in European Union countries, pharmaceutical prices are regulated by governments to force down the prices to levels roughly half those in the United States. And in Japan, with its even smaller population, drug prices are one-quarter their United States equivalents. Malaria, tuberculosis and AIDS affect many poor countries that have even less reason to pay a proportional share of development costs than do Europe and Japan.

Aside from these sunk-cost and global-public-good problems, some governments do not put much priority on obtaining and distributing vaccines for political reasons. Because vaccines have widely distributed benefits, they receive less political support than expenditures benefiting more concentrated, well organized groups. For example, building a hospital largely benefits those living nearby, so residents will lobby for the hospital.

The debate over pricing of antiretroviral drugs to treat AIDS illustrates the conflict between the goals of promoting R&D and treating a large share of the afflicted – a conflict that exists when intellectual property rights provide the only form of incentives for R&D. These issues came to a head when South Africa and Brazil fought for the right to license production of AIDS drugs without consent from the patent holders. As a result of public outcry, Washington dropped its efforts to champion drug company rights in these two countries. Pharmaceutical firms, faced with a public relations nightmare, eventually cut prices in least-developed countries to zero- or negative-profit levels.

Whatever the overall benefits of decisions regarding compulsory licensing of generic versions of AIDS drugs, it seems clear that phar-

maceutical developers will see this as setting a precedent that poor countries may use to obtain vaccines and drugs at low prices in the future. In these circumstances, pharma may



be reluctant to invest heavily in drug or vaccine research for diseases that primarily affect developing countries.

The world needs new institutions that both encourage new pharmaceutical development and provide the poor with access to these new drugs. Such institutions would ideally address both time-consistency (sunk-cost) and free-riding problems.

The world cannot wait until a vaccine is almost ready for production to address these issues. Rather, it is necessary to put in place incentives for R&D up front in order to motivate vaccine developers. The free-riding problem suggests that individual countries acting in narrow self-interest will not solve the problem. Solutions will have to come from entities addressing disease problems in the developing world as a whole.

PUSH AND PULL

As noted earlier, analyses of research incentives distinguish between push programs, which subsidize research inputs, and pull

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programs, which reward developers for research outputs. Examples of push programs include grants to academics, public equity investments in product development, R&D tax credits, and work in government laboratories. Pull programs could commit themselves in advance to finance the purchase of new vaccines and make them available to the people who need them.

The R&D system for developed countries, which has been very successful in generating new products, involves a combination of push and pull. Government organizations like the National Institutes for Health support basic research, and the private sector is stimulated to turn these into usable products by the promise of the market.

Applying the principle to vaccines and drugs for developing countries would suggest using push programs for basic research and pull programs to encourage applied research. A number of push programs are currently supporting research on diseases of the poor, including the International AIDS Vaccine Initiative, the Medicines for Malaria Venture and the Malaria Vaccine Initiative. In contrast, there are no programs in place to reward developers of effective malaria, tuberculosis or HIV vaccines.

Used on their own, push programs have a mixed record. On the one hand, some programs, like the development of a vaccine for meningococcal meningitis, have been successful. On the other, there have been some notable failures. For example, in the 1980s, the U.S. Agency for International Development invested considerable effort and millions of dollars in research for a malaria vaccine. Instead of a vaccine, the program yielded only a dramatic illustration of the problems with the push approach.

USAID initially funded one research team

that developed a candidate vaccine. Tests found that only two of nine recipients were actually protected from malaria, and suggested that the vaccine had serious side effects. Yet these mixed results led USAID to claim a “major breakthrough in the development of a vaccine against the most deadly form of malaria in human beings. The vaccine should be ready for use around the world, especially in developing countries, within five years.” That was in 1984.

Early work by a second team yielded even more disappointing results. But the project was funded despite the recommendations of expert reviewers. Once the grant came through, the principal investigator transferred funds to his personal account. He was later indicted for theft.

The independent evaluations of a third proposal found it both mediocre and unrealistic. However, the USAID project director ignored the report and arranged for the project to be fully funded. The principal investigator and his administrative assistant were later indicted for diverting money from the grant to their personal accounts. Just before his arrest, the Rockefeller Foundation provided the principal investigator with a \$750,000 research grant and USAID announced it was giving him an additional \$1.65 million. By 1986, USAID had spent more than \$60 million on its malaria vaccine efforts, with little to show for it.

The USAID malaria example is extreme, but it illustrates a number of general problems with push programs. Because they pay for research rather than results, decisions must be made about where to commit funds before a product is actually developed. Moreover, these decisions must be made by people who either do not have full information or who must rely on information from those with vested interests in the decisions.

In general, researchers funded on the basis of an outsider's assessment of potential, rather than for actual product delivery, have incentives to report overly optimistic assessments, and even to divert resources from the search for the desired product. Normally, this would not take the form of theft. But push-funded researchers may devote effort to other

oped. In the preceding decade, fewer than 10 were introduced.

Or consider the effect of the 1993 decision under which Medicare covers the full cost of flu vaccinations – a decision that substantially enlarged the expected market for such vaccines. The best flu vaccines in existence at the time the policy was implemented had an effi-

Individual countries acting in narrow self-interest will not solve the problem. Solutions will have to come from entities charged with addressing disease problems in the developing world as a whole.

projects rather than toward the sometimes-tedious work in developing a usable vaccine. Similar incentive problems arise if push funds come in other forms – for example, R&D tax credits for research or government investments in private research programs in exchange for a commitment to price the product at a low level.

By contrast, other historical examples suggest that pull programs in which public policies increase the value of markets for pharmaceuticals can spur effective R&D.

Consider America's Orphan Drug Act, which went into effect in 1983. It created a variety of financial incentives for companies to develop drugs for orphan diseases like Huntington's, ALS (Lou Gehrig's disease) and muscular dystrophy that each affect less than 200,000 Americans and therefore have limited markets.

The act provides grants and tax credits for clinical development and testing of orphan drugs. But its primary draw for pharmaceutical companies is a promise of seven years of market exclusivity. Since the act was passed, more than 200 orphan drugs have been devel-

cacy rate of 58 percent. Since then, more-effective vaccines have been introduced, including the first intranasal vaccine, which has an 85 percent efficacy rate in healthy adults. The resulting reduction in flu, post-1993, is expected to produce annual health benefits of close to \$6 billion.

From the perspective of the funders, a key benefit of pull programs is that they pay only for results. This means government officials or foundations do not have to worry that they are investing millions in projects that fail. Indeed, they do not even need to decide which scientists are most capable of developing the vaccines, which scientific approaches are most promising or even for which diseases the science is most ready for vaccine development. Pull programs efficiently align incentives, with governments and nonprofit funders defining the problem as commercial developers compete to design the best solution.

Another advantage of pull programs is that they encourage researchers to focus on the job at hand. Many academic and government researchers have career goals and intellectual interests that drive them away from

MAKING VACCINES PAY

the nuts and bolts of innovation. The later stages of product development include activities that are not particularly interesting but require considerable time and effort. Techniques for manufacturing sufficient quantities of candidate vaccines at a sufficient level of purity must be developed, animal models for the disease must be created, and product trials must be conducted. Nobody wins a Nobel Prize for these critical steps. But by linking payment to results, pull programs do provide strong incentives to researchers to concentrate their efforts on developing workable technology suitable for commercialization, rather than on publishing academic articles or preparing the next grant application.

Yet another advantage of pull programs is that they would help avoid budgetary conflicts between current health measures and the R&D needed to develop long-term solutions. Because no expenditure is incurred until the vaccine is available, governments can concentrate current spending on immediate needs, while committing themselves to spend future budgets on vaccines.

DESIGNING A PULL PROGRAM

Legally binding commitments to finance vaccine purchases for poor countries may be the most attractive form of pull programs. Alternative pull-type incentives can introduce their own distortions or are less efficient. Extending patents on other pharmaceuticals to reward developers of new products, for example, would place the entire burden of financing new products on the people who need the old pharmaceuticals. Increasing prices for current vaccines without explicit incentives for developing new vaccines would be an expensive and potentially ineffective way to spur new research.

The higher the price offered and the larger

the market, the more research will be undertaken, and the sooner a vaccine is likely to be developed. However, guaranteeing \$20 per person for the first 250 million people vaccinated, subject to a 10 percent co-payment by developing countries or other donors, would provide a market that would attract the attention of biotech and pharma. Purchasing a malaria vaccine at this price would be one of the most cost-effective health interventions available, saving more lives than virtually any other use of the funds. The manufacturer could be required to make the vaccine available at much lower prices after the first 250 million people were immunized. The guarantee should be structured as a legally binding contract and should be limited to vaccines judged safe and efficacious by existing regulatory agencies, like the FDA or its counterparts overseas.

MOVING FORWARD

The idea of pull-based incentives for vaccines has broad support. For example, in Europe, it has been endorsed by high-profile policymakers, ranging from Britain's chancellor of the exchequer, Gordon Brown, to Germany's foreign minister, Joschka Fisher. In the United States, the vaccine-commitment approach has appeal across a wide ideological spectrum because it adopts a market-based approach to deliver benefits to some of the world's poorest people.

Thus, the Clinton Administration proposed a pull program aimed at HIV, tuberculosis and malaria vaccines. And legislation incorporating the approach was introduced in Congress by leaders of both parties, including the Senate majority leader, Bill Frist, and the House minority whip, Nancy Pelosi. The Bill & Melinda Gates Foundation has commissioned the Center for Global Development to establish a working group (of which I am



Activist groups obtain more publicity and funds by attacking pharmaceutical companies than by advocating better incentive systems.

co-chairman) that is seeking to establish practical policy proposals for moving ahead.

To date, however, no commitment has been put in place to finance purchases of vaccines, provided they are developed. This is in part because there is no ready-made political constituency with a strong interest in lobbying for it. After all, foreign aid and government science agencies exercise greater influence in push programs than in programs that create open competition within the private sector. Pharmaceutical firms may generally welcome a purchase commitment, but benefit more immediately from push programs, like R&D tax credits. For their part, activist groups obtain more publicity and funds by

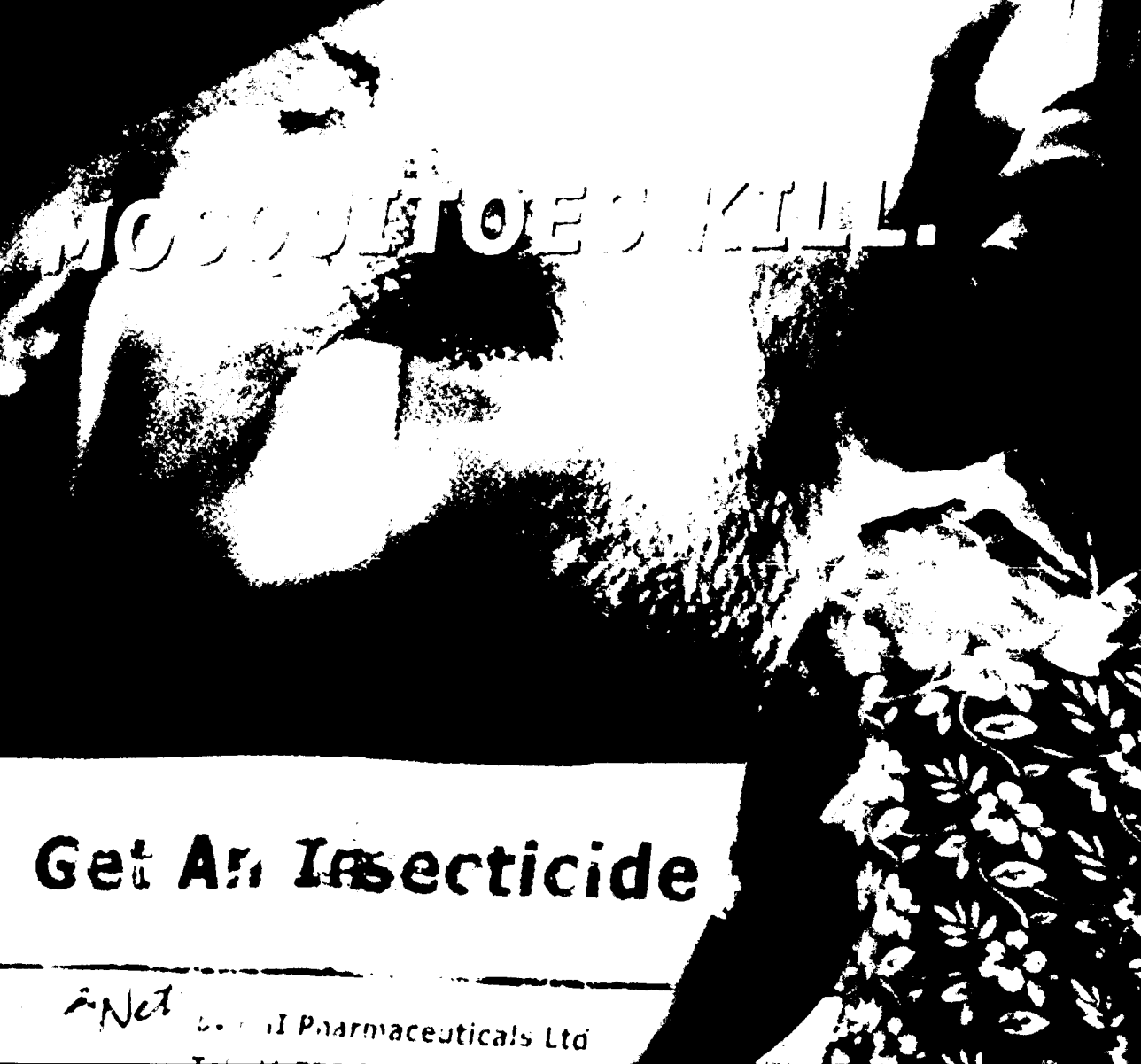
attacking pharmaceutical companies than by advocating better incentive systems.

Commitments to purchase vaccines could be undertaken by credible entities like the governments of rich countries, international institutions like the World Bank, private foundations like the Bill & Melinda Gates Foundation or by some combination thereof.

The World Bank could commit to provide subsidized loans to any member country that wanted to purchase the vaccine, as long as prespecified terms were met. The Bank could also sweeten the standard terms of such loans for vaccine-purchase commitments by providing part of the purchase price through grants. Alternatively, other donors – private foundations or governments – could provide subsidies by committing themselves to buy down loans. In other words, they would give the member the money to repay the loan, as was done in Nigeria's polio-eradication campaign.

The process of creating large, credible commitments to a market for vaccines won't be easy, and it certainly won't lack risks.

But the alternative – a status quo in which millions die annually from malaria, tuberculosis and HIV, and vaccines against these diseases remain a low priority for most pharmaceutical firms – is simply not acceptable. By offering to help buy vaccines against these diseases if they are developed, a program sponsor could harness the inventiveness the private sector has shown in confronting diseases common in developed countries and direct it toward addressing the health needs of the world's poor. If such a commitment fails to induce the development of the needed products, no funds will be spent and no harm done. If it succeeds, millions of lives will be saved each year. 



MOSQUITOES KILL.

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KILL MOSQUITOES

Malaria.

Malaria ranks among the major health and development challenges primarily (but not exclusively) facing developing countries. Endemic in 91 countries that account for 40 percent of the world's population, malaria affects an estimated 300 million people. And though in most cases the disease is treatable, it is responsible for more than one million deaths annually. In sub-Saharan Africa, the most affected region, malaria-related illnesses claim the life of one out of every 20 children below the age of 5. Mortality rates are lower for adults, but frequent debilitating attacks reduce the quality of life for chronic sufferers.

Putting a dollar figure on the human cost of this terrible disease is very hard. But it is possible to calculate the far smaller tangible costs associated with reduced productivity

First Quarter 2004

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in the countries affected. And these estimates, in turn, offer a sense of just how valuable a vaccine (or other measures for eradicating malaria) would be. Our back-of-the-envelope calculations imply that the cost of delaying the eradication of the disease by even a few years could run to tens of billions of dollars.

THE DISEASE

Malaria is a parasitic disease transmitted by anopheles mosquitoes. Risk of infection is partly driven by factors outside individual control, such as the fraction of the mosquito population that carries the parasite, the life expectancy of the mosquito relative to the parasite's incubation period, and average ambient temperature. Individual risk can be reduced, however, through a variety of measures – for example, using bed netting (most mosquito bites occur between sunset and sunrise) and staying two miles (the insect's range) from mosquito breeding grounds.

The fact that infection risk depends on both environmental conditions and behavioral responses translates into a wide variation in exposure from place to place. The average number of infective bites per person per year ranges from zero in nontropical areas to the low single digits in the subtropics, but the number jumps to between 40 and more than 100 bites in some tropical areas. Among regions, sub-Saharan Africa suffers the highest exposure rates, followed by parts of Asia and Latin America.

Over time the human immune system adjusts to the parasite, resulting in fairly low adult mortality in endemic areas. Mortality is

concentrated among (a) children between the age of six months (the age at which immunity endowed by the mother wanes) and five years (the age at which children develop their own immunity), (b) travelers and migrants from nonmalarial regions, (c) populations in previously nonmalarial regions undergoing climate change and (d) populations with repressed immune systems, including pregnant women and people with HIV.

A typical bout of malaria lasts about 10 to 14 days, with four to six days of incapacitation and recuperation periods of four to eight days characterized by fatigue and weakness. Mild malaria usually leads to one or two episodes of fever per year, coupled with headache, nausea, fatigue and diarrhea, with relatively few side effects between episodes. Severe malaria results in impaired consciousness, weakness, jaundice and, in some cases, death.

COMBATING MALARIA

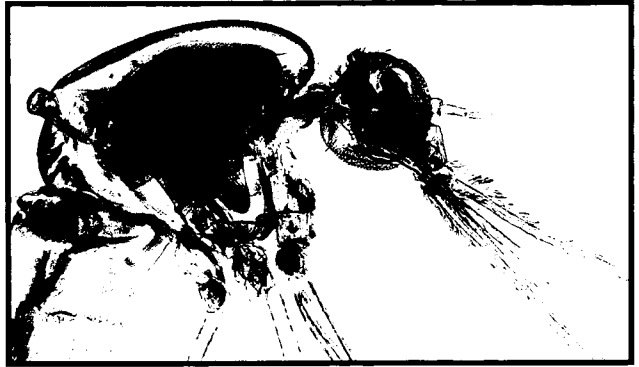
The human and economic costs of malaria have been recognized for centuries. The discovery of the transmission mechanism in the late 19th century opened the way to systematic anti-malarial efforts. Attempts at defeating malaria have followed four distinct routes: reducing the mosquito population, minimizing the number of infective bites for a given mosquito population, developing anti-malarial drugs and developing an effective vaccine.

Early post-World War II efforts focused on eradicating mosquitoes. Widespread use of DDT coupled with the coating and draining of breeding grounds resulted in a substantial reduction in malaria morbidity in the subtropics, notably southern Europe and parts of Asia (Malaysia, Singapore) from 1940 to the late 1960s. This fueled optimism that malaria could be rapidly eradicated.

Alas, these successes did not extend to areas with higher incidence, notably sub-

DESMOND MCCARTHY is a consultant to the World Bank. HOLGER WOLF and YI WU teach at Georgetown University. This paper draws from their World Bank working paper, "The Growth Effects of Malaria." The views expressed herein are not necessarily those of the World Bank.

The parasite's foothold in the tropical parts of Africa was barely disturbed in the first half of the 20th century, with mortality declining only moderately before rebounding in recent decades.



Saharan Africa. And as the environmental side effects became better understood in the late 1960s, they were largely terminated. Subsequent efforts focused on the reduction of human exposure to mosquitos – notably through the use of insecticide-impregnated bed nets and reduction of local breeding grounds.

Better medical treatment provides the second pillar of current anti-malarial efforts. Progress on the medical side has been problematic, however. Effective anti-malarials capable of eliminating parasites in the blood (though not in the liver) have been developed. Most are both effective and relatively cheap (\$1 to \$5 per bout). However, the disease has not stood still. Premature termination of treatment cycles by patients and partial mosquito eradication efforts have allowed the parasite and the mosquito to evolve, leading to greater resistance to commonly used drugs and insecticides.

There are grounds for optimism that the behavior- and treatment-focused pillars will soon be complemented by vaccines. Currently, active programs include the World Health Organization's Medicines for Malaria Venture (a joint public-private initiative that aims to

develop anti-malarial drugs), the Malaria Vaccine Initiative (financed by the Bill & Melinda Gates Foundation with the objective of accelerating the clinical development of candidates), and the P. Falciparum Genome Sequencing Consortium of the Sanger Center, the Institute for Genomic Research/Naval Medical Research Institute, and Stanford University.

WHERE WE STAND TODAY

In much of the world, the threat from malaria has faded: outside sub-Saharan Africa and some areas in Asia and Latin America, mortality rates have plummeted to near zero. But the parasite's foothold in the tropical parts of Africa was barely disturbed in the first half of the 20th century, with mortality declining only moderately before rebounding in recent decades. In some countries, one-quarter of the population is thought to be infected.

Equally worrisome, the sustainability of the decline outside sub-Saharan Africa is now in question. While medical advances, notably an effective vaccine, promise further reductions, climate changes combined with the increasing mobility of both mosquito and human populations threatens to increase the

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susceptible area. "Airport malaria," the infection of individuals living close to airports, is perhaps the best known instance of the mobility effect, though the number of cases is thus far small.

MALARIA AND DEVELOPMENT

In the last few years, the links between disease and economic development have attracted increased research attention from, among others, a group of researchers around Jeffrey Sachs at Columbia University. These linkages are two-directional.

An important link runs from development to improved health. Economic development is likely to reduce the incidence of a variety of easily preventable diseases by funding public investment in sanitation and public health care, and by giving households the resources to invest in preventive measures and to obtain medical treatment. Poorer countries also tend to suffer from a relatively higher incidence of conflict, economic crises and administrative disorganization, which disrupt health services.

A second causal chain runs into the opposite direction: reductions in malaria increase productivity, creating a positive feedback effect. How important are these linkages? On the most direct level, malaria incapacitates part of the labor force. This loss of labor input has been the primary focus of the classic studies of malaria's economic impact dating to before World War II, and the approach has been refined in several careful case studies since.

The estimates suggest that attacks entail a loss of four or more working days, followed by additional days with reduced work capacity. The output effect of the lost work time depends both on the degree to which other family members can temporarily fill in and

on the overlap between malaria episodes and harvest periods when labor is most productive. A second effect operates longer term: malaria is a major cause of school absenteeism. Furthermore, malaria appears to impair learning capacity, reducing the accumulation of human capital.

The incapacitation of the labor force in turn affects the attractiveness of a locality as an investment site, leading to reduced capital accumulation. Endemic malaria also reduces the growth potential for some industries – notably tourism – and sharply raises the cost of infrastructure projects and other collective enterprises.

Indeed, early anti-malaria measures in Panama were partly motivated by the need to protect workers building the canal. Malaria has also been cited as a major obstacle in building the trans-Amazonian highway, as well as major dams and tourism projects.

These direct effects on labor and capital are augmented by a range of indirect effects on productivity. Frequent absenteeism reduces the efficiency of the informal networks organized around work activities, requiring greater redundancy and reducing the scope for specialization.

Malaria-motivated limits on mobility (both domestic and international) make it more difficult to match skills to work demands. Changes in planting patterns to minimize the overlap between malaria episodes and peak agricultural work times reduce agricultural productivity.

Areas with high malaria incidence may thus experience lower trend growth. While the simple correlation between growth rates and malaria incidence does not establish causal direction, the presence of a linkage is evident. As the table shows, the third of countries with the highest malaria morbidity rates has the lowest median GDP per capita, the



lowest growth rate, the lowest investment rate and the lowest school enrollment ratios.

While the individual costs of malaria in terms of days of work lost and treatment costs can be measured fairly accurately, estimating the aggregate economic costs is more difficult, as it requires assessing indirect costs – education never received, tourism and infrastructure forgone, industrial specialization patterns never pursued. They can, however, be indirectly captured in cross-country studies. If malaria exerts an adverse effect on growth, one would expect to find an explanatory role for malaria in statistical analyses that estimate the impact of various factors affecting growth.

Jeffrey Sachs and his colleagues have pursued this approach. Their measure of malaria is an exposure index, defined as the fraction of the population at risk multiplied by the fraction of malaria cases of the most serious type. Their results reveal both a significant negative correlation between malaria exposure and income per person, and a significant positive association between declines in malaria exposure from 1965 to 1994 and the



GROWTH DETERMINANTS FOR COUNTRIES WITH LOW, MEDIUM AND HIGH MALARIA MORBIDITY

	Low	Medium	High
Malaria morbidity (per 100,000)	30	574	6,697
GDP per capita (Start of Period)	3,595	2,193	1,267
Average GDP p.c. growth rate (5Y)	1.45	1.51	0.22
Investment ratio	22.7	20.0	18.3
Primary school enrollment index	104	99	76
Secondary enrollment index	49	35	16

1965–1990 per capita growth rate. They estimate that malaria may reduce growth by more than 1 percentage point a year.

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We pursued a related approach, but use World Health Organization data for malaria morbidity. Our estimates suggest that eliminating malaria could increase growth by more than 0.25 percentage points per year for about a quarter of the sample countries. These findings are more conservative than earlier GDP growth loss estimates of between 0.6 percentage points and 1.3 percentage points. But by any absolute measure, the numbers are frightfully high.

COST PER DISABILITY-ADJUSTED-LIFE-YEAR SAVED (IN \$)

INTERVENTION	COST PER DALY SAVED	PERCENT INCREASE OF HEALTH BUDGET
Better access to 2nd and 3rd line drugs	\$1.4	0.3%
Better compliance with drug therapy	4.0	0.5
Insecticide treatment of existing nets	6.0	3.0
One spraying round per year	22.0	27.0
Chloroquine prophylaxis	43.0	0.2
Distribution and treatment of nets	44.0	24.0

SOURCE: WHO (1999:57). DALY: Disability Adjusted Life Year. The health budget baseline is the public sector health budget for a typical low-income sub-Saharan country.

It is notoriously difficult to put a dollar figure on the “cost” of disease. Illness has many aspects, ranging from the psychological to the economic. If one restricts attention to direct economic effects, though, it is possible to provide a rough estimate of the cost of malaria.

If we take our estimated growth reduction of 0.25 percent and the median income level of the high malaria group of \$1,267, the annual cost per individual (in the sense of forgone income growth) comes to \$3.17. As long as malaria persists, these annual costs must be added to the previous years’ costs, leading to a large cumulative effect. Taking the current trend rate of economic growth – a wretched 0.22 percent – GDP per capita can be expected to grow to \$1,339 over 25 years.

Raising this growth rate by 0.25 percentage points – the estimated gain from eradicated malaria – would raise the GDP per capita over 25 years to \$1,425. While this amounts to only a 6.4 percent income gain, an increase of \$86 per person multiplied by a conservative 500 million individuals living in malaria endemic areas implies that the failure to eradicate malaria today means that the GDP of the most affected area will be \$43 billion smaller in a quarter-century than it would have been.

These are, of course, very rough calculations abstracting from a range of other factors. But they do provide a sense of the magnitudes involved. Note, too, that this estimate is conservative: increasing the population assumed to live in affected areas or raising the assumed growth cost could lift the forgone output substantially.

Moreover, these cost measures do not include the resources spent on combating malaria. Anne Mills has estimated these costs at more than 1 percent of income in six sub-Saharan countries. Were these resources instead to be devoted to human and physical capital accumulation, the growth effect would be further enlarged.

COPING WITH CATASTROPHE

Over the course of the 20th century, humankind succeeded in beating back a number of previously pervasive diseases. The success in combating malaria has to date been more mixed, with near complete success in some areas, but slow progress in others – in particular, those climatically best suited to the transmission of the disease.

The not-impossible dream of virtually eliminating malaria lies in finding effective vaccines. The figures reported above establish that even on the most narrow economic cost calculations, the payoff to a vaccine would be astronomically high.



Drug Distribution

Putting the Pieces Together

BY LAWTON BURNS
AND PATRICIA DANZON

This selection from *The Health Care Value Chain** is more technical than most book excerpts published in the *Milken Institute*

Review. The authors, Lawton Burns and Patricia Danzon of the University of Pennsylvania's Wharton School, are specialists in health care economics and management, and have assembled detailed portraits of how the business works. The point of excerpting their nuts-and-bolts analysis of the complex relationships between pharmaceutical makers and their biggest clients is to give readers an idea of the forces driving supply, demand and innovation in the \$100 billion-plus market for drugs.



With medical technology and medical care changing rapidly, the capacity of workaday institutions to support the rapid diffusion of life-saving technologies is becoming increasingly problematic.

— Peter Passell

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Pharmaceutical products are a major category of health care costs.

In 1999, retail prescription drugs accounted for \$99.6 billion, more than 8 percent of national health expenditures. These figures do not include drugs sold in institutional settings like hospitals, which are estimated to account for 25 percent of total pharmaceutical sales and 10 to 15 percent of prescription drug costs. Drugs purchased through integrated delivery networks (IDNs for short) represent 15 to 23 percent of contracted supply expenditures and total an estimated \$13 billion to \$15 billion annually. Taken together, pharmaceutical sales for 1999 were roughly \$122 billion.

Moreover, retail drug outlays have been increasing much faster than other components of health care, rising 16.9 percent between 1998 and 1999. Thus, drug sales in the United States have been growing faster than GDP. A primary driver is increased volume, which itself is due to a combination of factors – the substitution of drugs for non-drug therapies, the aging of the population, the introduction of new pharmaceutical products and product formulations, and the changing mix of products used.

Rising drug costs have attracted a lot of attention from the payers and providers of health care, as well as from their purchasing agents – the HMOs acting on behalf of employers and government, and the group-purchasing organizations (GPOs) acting on behalf of hospital systems. Buyers and their agents have consolidated and become more aggressive purchasers of these products.

Since the 1980s, several key features of the industry's structure have changed, engender-

ing greater competition. Generic drug manufacturers have grown in prominence, by 1998 accounting for 45 percent of drug units sold (but 19 percent of revenues). Their ascendance is in part a consequence of the Waxman-Hatch Act of 1984, which exempted generic drugs from clinical trials and virtually eliminated the period between patent expiration and the market entry of generics. Generics have also grown due to Medicaid's and HMOs' refusal to pay more than the price of generics, leaving patients to pay the additional cost to get branded drugs.

At the same time, the industry has been consolidating. Between 1990 and 1999, the top four pharmaceutical firms increased their combined worldwide market share from 14 to 22 percent, while the share of the top eight firms grew from 24 to 38 percent and the share of the top 30 grew their share from 57 to 70 percent. Similar figures hold for the U.S. market. Normally, consolidation reduces rivalry in an industry. However, with pharma-

ceuticals, no single firm has more than a 7 percent market share worldwide. Moreover, as a result of the horizontal combinations, firms are more likely to have product lines that overlap.

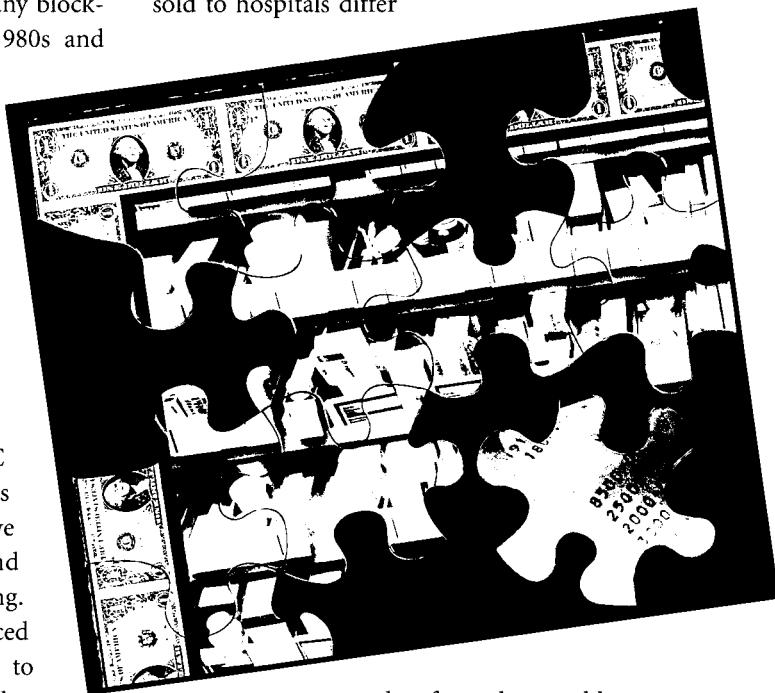
The expiration of patents of many blockbuster drugs introduced in the 1980s and 1990s has increased marketing competition, and given firms incentives to develop close therapeutic substitutes (so-called “me-too” drugs) or generic versions of each other’s products. The result is pervasive therapeutic and generic drug competition.

Finally, the rise of over-the-counter (OTC) medications has in some cases created a lower-priced alternative to branded drugs. OTC medications are subject to less expensive and less time-intensive FDA approval requirements, and fewer restrictions on their advertising. Their appeal to HMOs has induced many large pharmaceutical firms to enter the OTC market, selling less potent versions of their branded drugs.

Pharmaceutical firms compete in more than 20 therapeutic categories. In 1999, the top classes (based on sales) in the United States were central nervous system disorders (23 percent), neoplasms, endocrine system and metabolic disease (19 percent), cardiovascular system (19 percent), digestive and genito-urinary system (14 percent), respiratory system (11 percent) and infective and parasitic diseases (11 percent). Drugs sold to hospitals address a different mix of therapeutic areas. The top drugs sold in hospitals are used to treat clinical conditions such as anemia, bacterial infections, neutropenia, deep vein thrombosis and ovarian cancer, as well as to support procedures such as the installation

of vascular stents and balloon angioplasty.

The foregoing analysis suggests several important points. First, the hospital trade is only one market served by pharma, and it is certainly not the largest. Second, the drugs sold to hospitals differ



somewhat from drugs sold to other market segments. There can be overlap between hospital inpatient and outpatient markets, and between hospitals and specialty physician clinics (such as those for oncology). Third, pharmaceutical firms compete within therapeutic areas, though individual firms tend to dominate in one area or another based on their control of a blockbuster drug. Indeed, market concentration (as defined by share of prescriptions sold by the top four firms in individual therapeutic areas) tends to be quite high. Fourth, a firm’s competitors are not likely to be the same across all therapeutic areas. As a result, any sample of pharmaceutical firms provides only a limited perspective on the pharmaceutical market and supply chain.

SALES AND MARKETING ORGANIZATION OF PHARMACEUTICAL FIRMS

Sales and marketing account for a large portion of the pharmaceutical firm's costs – as much as 30 percent of sales in the early 1990s. Marketing is typically concerned with the firm's patented brands and their promotion, while sales refer to the firm's sales representatives (so-called “drug detailers”) who call on major accounts. A pharmaceutical firm will typically have hundreds of organized customers spanning the supply chain: federal and state governments, employers, HMOs, pharmacy benefit managers (PBMs), hospital systems and large medical centers, GPOs, drugstore chains, behavioral health organizations, home health organizations and wholesalers. The sales staff also calls on individual physicians. The number of detailers has grown dramatically due to the number of new products introduced over the past few years and an increased emphasis on competition through marketing.

Within their sales organizations, pharmaceutical firms often seek to separate business functions (such as contracting and negotiations) from clinical functions (such as relaying information on safety and efficacy). This is done to maximize the contact time between detailers and physicians, to develop the economic case for their drugs among customers, and to provide sales representatives a single point of contact within the firm to resolve business issues.

To accomplish this, they often appoint account managers for their large organized customers, who seek to represent all of the firm's brands with one face. They market the firms' products at each account by, in the words of one pharma executive, “accessing thought leaders, those people who help make the decisions regarding formulary contracting and the availability of our products.”

These managers also seek to coordinate their efforts with the managers and teams promoting individual drug brands to “clinical thought leaders,” as well as with the district managers for sales representatives serving those accounts.

Sales and marketing thus operate in a matrix structure. Some sales personnel focus on specific customer accounts, while others focus on specific brands and clinical products – with a defined corporate entity to integrate them. This entity is viewed as a solution to the growing complexity and differentiation in the firm's products and customer base. As part of this matrix, pricing and contracts are developed on a consensual basis between the account managers and the brand teams.

Sales procedures work differently for branded items than for generics. The customer for the branded items is typically the specialist physician in the relevant therapeutic area (for example, an oncologist for a cancer drug). Sales reps deal directly with these specialists to build acceptance for the drug and gain physician support for placement on the hospital formulary. With generics, the sales organization deals more with the GPOs and other organized buying agents in negotiating terms for a portfolio of products.

ILLUSTRATION OF CONTRACTING PROCESS

Pharmaceutical firms estimate that 90 percent of their products sold to the institutional market go through distributors. Sales of about 80 percent of the drugs going to institutions are negotiated with GPOs; there are only a handful of contracts with individual provider organizations that can perform at the same level as GPOs. Thus, to the extent that the drug company's sales portfolio includes a lot of products going to the institutional market, GPOs are important buyers.

Today, sellers push back more, ask them where we win in this deal, call their bluff and ask how we can increase shareholder value for both companies.



In the past, pharmaceutical firms dealt with GPOs using a bidding process and short-term contracts. Today, there are more long-term contracts and, reportedly, more partnership arrangements based on shared vision and goals. In practice, this can mean GPO efforts to move market share and increase compliance, to integrate information across their membership, and to understand how their providers use the pharmaceutical firm's products. Nevertheless, due to the overlap in the product portfolios of drug firms, GPOs often pit one manufacturer against another at contract negotiating time.

GPO size can also be an important factor in terms of negotiating discounts and rebates. For the same level of control, larger customers get better pricing; the customer with a higher level of control gets better pricing even if it is smaller in size. A GPO can end up contracting with more than one pharmaceutical firm in a given therapeutic area if the vendors differ in their contract requirements for control and the GPO can satisfy both sets.

In the past, when confronted with GPO demands for lower prices, some account managers promoted from the ranks of sales representatives would in the words of one industry analyst "try to keep everybody happy, buy them a cup of coffee and try to solve the GPO's problem." Today, sellers take a "more honest approach with GPOs – push back more, ask them where we win in this deal, call their bluff and ask how we can increase share-

holder value for both companies."

After the contract is signed, the GPO informs its institutional members about the terms and pricing. At the same time, the manufacturer publicizes the contract to its sales representatives, who then contact providers within these accounts to ascertain what they need to do to make the contracted drug available to patients. Some hospitals do not permit the sales representative to discuss a product unless it is on contract; others do not have such rules.

GPOs select the distributors that their members use. For their part, pharmaceutical manufacturers contract with all distributors to help increase the penetration of the products into the market. Manufacturers look to distributors for assistance primarily in the areas of "pick, pack and ship." They are viewed as "efficient order takers," efficient distribution points for bulk shipping that reduce the number of customers to be served, and proficient at multiple deliveries and just-in-time delivery.

In the market for branded drugs, wholesalers exert little influence on customer demand (and thus little on the manufacturer's business) since the products are "pulled" by clinicians rather than "pushed" by the distributors. While distributors might wish to exert influence over what drugs are ordered, they would encounter strong physician opposition. As a result, distribution is not an important topic to sales executives in pharmaceutical



firms concerned with branded drugs.

BRANDED VERSUS GENERIC DRUGS

The GPO's influence over the pharmaceutical manufacturer varies by type of product. For branded items where the manufacturer has the only candidate drug in that therapeutic area, the GPO and manufacturer negotiate a single-source agreement. While such drugs can be very expensive, the GPO will accede to the price when physicians within their member institutions want it. In such situations, the manufacturer has no incentive to offer discounts. For those with strong brand positions, GPOs are not important intermediaries. Instead, manufacturers use them as information channels to influence physicians.

Relationships between manufacturers and GPOs become more interesting when additional branded drugs enter the market in the therapeutic area. This is where negotiations become more pronounced and filled with threats of walking away from the table. This may be particularly true when the newer brands are much lower in price. The Lilly-

Centocor drug ReoPro, for example, is a monoclonal biologic product that costs \$1,300-\$1,500 per patient. The therapeutic alternative subsequently introduced by a competitor costs only \$400, but was "less efficacious" because (according to Lilly) it required more follow-up visits and was less effective in reducing patient mortality. The higher-cost drug becomes a target, especially if it accounts for a large percentage of the hospital's drug expenditures.

Finally, as drugs go off patent, they are faced with generic competitors and lower product prices. The generics enter the market at prices 40 percent to 70 percent of the market leader, whose price may remain unchanged. Generics typically capture 50 percent of sales within six months after patent expiration, and are typically purchased by GPOs as part of a multi-source arrangement with several vendors. Relationships with GPOs regarding generics tend to be less face-to-face and more based on telephone calls and occasional visits.

Generics tend to fall off the radar screen of the drug manufacturers. Most brand manufacturers have given up trying to enter this

market in the United States. They continue to sell their branded products to the shrinking “brand loyal” segment, but do not bother to promote them.

As their products – both branded and generic – can be purchased from multiple sources, manufacturers are forced to work more with the GPOs. Their avowed strategy is to have a continuous stream of innovative and sole-source products that clinicians want, and thus to lower the barriers to entry in the hospital market.

They say that GPOs do not drive drug sales, but on the other side of the coin can be a barrier for them. One barrier they pose is “counter detailing” – that is, disseminating publications that tout the advantages of competitors’ products. They thus try to work with the GPOs and “try not to inflame them.” The goal here is to keep the negotiations focused on more than just price – for example, on marketing attributes of the products.

Manufacturer-GPO bargaining situations can resemble a game of chicken in reverse, in which each side threatens to walk away. In essence, each tells the other, “You need us more than we need you.”

Manufacturers claim they do not need the GPO’s permission to access its hospitals. Indeed, they often negotiate agreements with large IDNs that are better than the deals negotiated by their GPOs. These deals may be prompted by financial problems at the provider system, often when HMOs press them for discounts.

The manufacturer is willing to negotiate more attractive terms with the IDN member because, in the words of one manufacturing executive, “while the GPOs preach a big game of being able to drive share, at the end of the day it is really the individual hospital that drives share.” The member may also design and implement the formulary.

Pharmaceutical manufacturers thus believe the competition between rival drugs is played out more at the integrated delivery network and hospital level than at the GPO level. Moreover, the larger IDNs are often shareholders in the GPOs and use their GPOs when it is to their convenience, but feel free to cut their own deals with manufacturers. In fact, they tell vendors, “We better not find out that you give our GPO a better deal than what we get here at our IDN.” At the same time, vendors rely on these IDNs for discretion in not divulging the contracts and terms to either their GPO or other IDNs.

Of course, the manufacturer’s willingness to go beyond the GPO contract may depend on the size of the IDN or GPO member that is seeking the additional discount. Pharmaceutical executives say that they don’t want to jeopardize a total GPO contract for just one system.

PRODUCT COST VERSUS TOTAL COST

Pharmaceutical executives believe that the current emphasis on cost containment poses an enormous barrier to the sales of their branded drugs. Hospital executives thus judge success by different criteria than pharmaceutical firms. Hospital executives are rewarded for reducing costs, while pharmaceutical firms are looking to increase market share and sales. They do this largely through innovation. They acknowledge that their new products are expensive and add costs to hospital systems. However, they argue that these products treat diseases in new ways that improve patients’ quality of life, or substitute for more expensive services such as hospitalization. Thus, the pharmaceutical firms argue that their new products frequently contribute to lower total costs.

Despite pressures for short-term cost reductions, pharmaceutical executives mention

several facilitators to disseminating the “total cost” message to GPOs and their hospital members. First, the message is reportedly more effective in some managed care markets (i.e., full-risk capitation, where patients are treated for a fixed annual fee) than in others (i.e., heavily discounted fee-for-service). Manufacturing executives say they strike better partnerships with systems oriented to care management and quality rather than just cost management. Such systems may be able to understand both their costs and outcomes.

Manufacturers often point to leading IDNs such as Intermountain as illustrations of this clinical orientation. They also fare well with IDNs in which the director of pharmacy reports to a clinical executive rather than someone in finance. Finance executives tend to “view pharmacy as a bucket of expense within the institution and often fail to compare the value of that bucket of expense with other buckets.”

Pharmaceutical executives say they also strike better partnerships with providers that are oriented to making process improvements based on utilization and outcomes data, and that are seeking to compete in their local markets based on a quality advantage. Such providers have a corporate philosophy of “being at the cutting edge of delivering the best patient care.”

WHO IS THE CUSTOMER?

Drug firms recognize four broad classes of customers: the payer (insurance company), the buyer (the entity selecting the product), the consumer (the patient) and the dispenser (the pharmacy). For branded items, firms clearly see the physician as the key buyer. Clinicians pull their products through the supply chain, based on their preferences; distributors and GPOs cannot push products in this context. For generic items, the GPOs may

be the more important buyers.

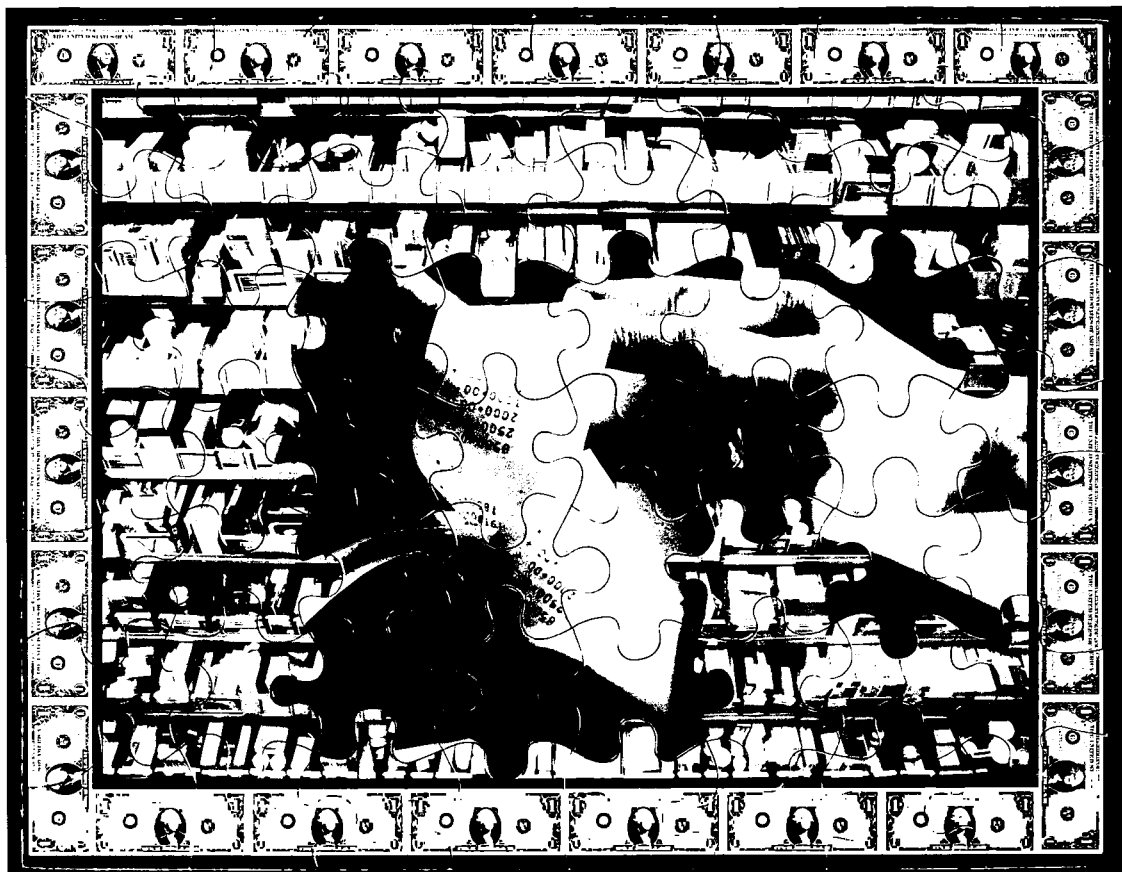
As with medical device firms, pharmaceutical companies maintain direct, continuing contact with physicians through sales reps in the field. They call on physicians in their offices and, for drugs used in procedures such as cardiac catheterizations, follow the physician into the lab. The customer is thus not only the specialty physician in the particular therapeutic area (such as the clinical cardiologist), but also interventional cardiologists in the cath lab, physicians in the emergency room and other specialists who treat cardiac patients. Besides physicians, other customers include nurses and clinical pharmacists.

Non-clinicians may also be customers when there are issues regarding price or where there is direct contracting between the pharmaceutical firm and the IDN without a GPO as intermediary. In such cases, the customers can be administrators and directors of pharmacy and materials management. Finally, pharmaceutical firms recognize that the federal government’s Health Care Financing Administration (HCFA) is a customer, based on its prominence as a payer.

INTEGRATED DELIVERY NETWORKS

Pharmaceutical firms view IDNs in slightly different ways than do other players along the health care supply chain. On the one hand, pharmas like to see GPOs and their member IDNs have certain standardized features, such as contracting compliance, communication of new product and contract information to hospital members, data collection and reporting, the development of care practices and protocols, and other similar means of “managing their institutions in a consistent way that makes it easier for [pharma] to do business with them.”

Moreover, they see opportunities for improved sales to hospitals that belong to sys-



tems. For example, Lilly's drug ReoPro had traditionally been used in the central cardiac cath lab of the flagship hospital of a local IDN. However, Lilly noticed that their drug was also being used with another drug to treat heart attack victims in the IDN's outlying hospitals. An integrated system is valuable to a manufacturer when the system as a whole stocks its drug in all of their facilities, and also helps to define the protocols for the drug's use.

In addition, drug makers value a hospital system with a good communications network (for example, Internet linkages and satellite video conferencing) that can allow them to access the system's hospitals to make joint presentations about their products, as opposed to reaching each facility individually.

On the other hand, standardization of activity is sometimes synonymous with com-

moditization. Accordingly, pharmaceutical firms prefer to see purchases driven by clinical preferences expressed in the patient-physician relationship and aggregated up to the hospital and GPO level, rather than imposed by the GPO on clinicians down below.

Manufacturers thus recognize variations in preferences both within and between IDN members of a GPO. Some institutions may be more focused on the cost issues of the particular drug, while others may be more oriented to quality and total cost. As a result, pharmas are not entirely sold on the ability of IDNs, let alone GPOs, to do committed purchasing of branded drugs.

They say that some IDNs want a standardized, discounted price for every entity in their systems, but not every entity possesses the capability to deliver in terms of compliance. They state they would like to contract with

IDNs that have homogeneous members and common goals as to how they position themselves in the marketplace. They point to the investor-owned systems as examples of member homogeneity, although some of these systems are too focused on price for their liking. They also point to some non-profit IDNs that try to differentiate their hospitals as clinically superior or convenient. Such hospitals are reportedly easy to do business with.

Overall, however, manufacturers state there are not a lot of partnerships with GPOs and their member IDNs. The IDNs are “confused” and “unimpressive.” When asked to name names, most executives were hard-pressed to identify more than three or four IDNs that behaved as integrated systems.

Manufacturers also believe the IDNs have needs that are too individual to bundle into a GPO platform, although it may be possible to develop programs to meet the needs of regional groups within a GPO or IDN. In addition, the manufacturer (through its account group executive team) is trying to relay a message about the combined clinical and economic benefits of its product, and is confronted with a buyer with fragmented decision making.

As one executive expressed it, “There are too many hands in the cookie jar.”

The situation is even more difficult if the IDN has developed an insurance vehicle or other elements of the continuum of care (such as physician practices). For example, physicians within one IDN may compete with one another. One IDN can partner with multiple cardiology groups to work its catheterization lab, and those groups can have totally different preferences for drugs. This makes it hard to standardize within a market.

Similarly, a hospital with its own insurance company typically executes a separate contract with the pharmaceutical manufacturer.

This is due in part to the lack of integrated purchasing between these two entities. It is also due to the fact that the HMOs purchase more branded products while the hospitals purchase more generic drugs. Finally, the different contracts reflect the reality that HMOs can influence prescribing and utilization more directly than can hospitals through their formularies. While both HMOs and hospitals have formularies, they exert different levels of control.

Vertical integration and other efforts to develop a continuum of care have also added great complexity to IDNs, which make it hard for manufacturers to deal with them. First, IDNs bundle and then unbundle components. One day they are integrated, the next day they are disintegrated. In the manufacturer’s eyes, “that just creates a whole bunch of chaos in the contracting process.”

At the same time, executives state that providers will only get the same deal as a GPO if they can deliver the market share. Second, GPOs tend to present to manufacturers defined purchasing contracts (buckets) for hospitals, for physicians and alternate care sites and so on. By contrast, IDNs blur these distinctions, then ask for contracts that span the continuum and require each provider to state the same price.

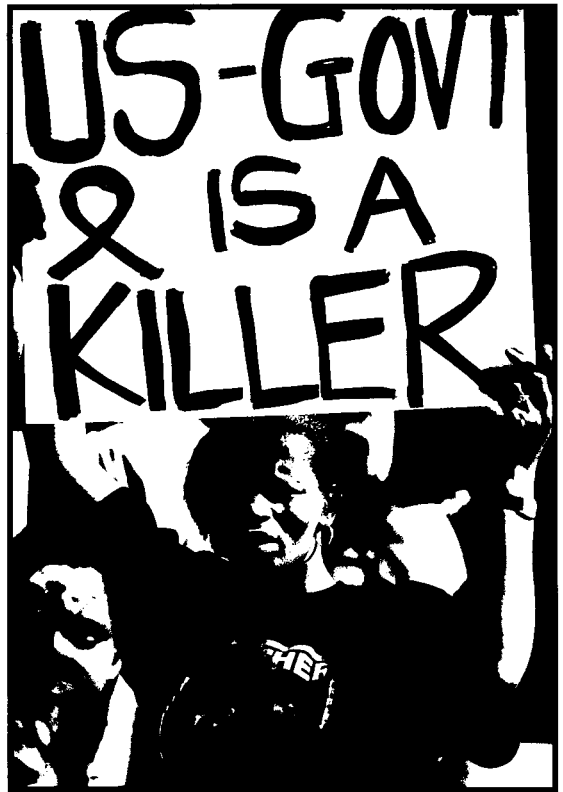
One area where pharmaceutical manufacturers express a desire for closer collaboration with IDNs is coordination of clinical research. Manufacturers view IDNs and centers of excellence as possible partners in the development and clinical testing. Thus, even if the manufacturer does not have any blockbuster products currently serving the hospital market, its pipeline may contain such drugs. Any partnerships with IDNs are likely to be based on that IDN’s scientific expertise or experience with a given disease and are not going to be across the board. 

BY JEAN O. LANJOUW

For many years, governments, drug companies and a variety of advocacy groups have been battling over patent protection for pharmaceuticals in poor countries. In particular, the fight involves the standards required for membership in the World Trade Organization – requirements known as Trade-Related aspects of Intellectual Property, or TRIPS, rules. These provisions were a source of bitter controversy during the Uruguay round of trade negotiations in the 1980s.

The pharmaceutical industry resolutely insisted that worldwide protection was crucial to sustain research on drugs. Poor countries, for their part, were equally adamant that patent rights should not limit their ability to produce or buy lower-cost generic versions for their own local markets. In the mid-1990s, the force of the AIDS epidemic moved this controversy out of the obscure realm of trade negotiations and onto the front pages of the newspapers as a major health and economic development issue to be fought out in the public arena.

Today, that sense of urgency has waned. Rich countries are beginning to earmark signi-



ficant funds to purchase antiretroviral drugs, used for treating AIDS, for distribution to low-income countries. And last August, on the eve of the WTO ministerial meeting in Cancun, an agreement was reached on rules governing the export of drugs under compulsory license to supply countries lacking the

JENNY LANJOUW is a senior fellow at both the Brookings Institution and the Center for Global Development in Washington, and is an associate professor in the agricultural and resource economics department at the University of California (Berkeley).

BIG IDEAS

ability to manufacture their own. Meanwhile, GlaxoSmithKline and Boehringer Ingelheim announced that they would license the production of their patented antiretrovirals for distribution in South Africa – ground-zero of the AIDS pandemic.

Thus, after years of frustrated efforts to reach a sensible resolution to the patent controversy, it is now tempting to declare victory and turn to other policy challenges. There are, after all, many barriers to drug access in poor countries ranging from income to transportation to health care infrastructure, and it may seem a distraction to continue arguing over protection of intellectual property rights.

Not quite. Moves to increase access to life-saving drugs are surely good news, but the patent problem has hardly been solved. The complex and uncertain rules that define the current system for protecting intellectual property will continue to be a source of international tension. And it would be a shame to let reforms drift off the proverbial radar screen. Building health infrastructure in poor countries will never be easy – it will take time and sizeable resources. Improving the patent system just takes political will.

WHAT IS THE CURRENT SYSTEM?

Some developing countries that are members of the WTO have until January 2005 to implement TRIPS standards; others have until January 2016. The Doha Declaration on the TRIPS Agreement and Public Health, issued two years ago, allows a specified group of “least developed countries” to defer, or not enforce, pharmaceutical patent rights for more than a decade. Taking advantage of these opportunities for extension, however, is at the discretion of individual nations’ governments, and some countries have been urged to choose faster implementation.

Cambodia and Nepal, the first of the least developed countries to join the WTO after its creation, did not opt for the extension, instead agreeing to a 2007 date.

Moreover, some countries are being pressed to implement so-called “TRIPS-plus” provisions that extend beyond the WTO minimum standards as the price of invitations to bilateral trade deals with rich countries. The tensions involved in this process are perfectly captured in the 2002 law that set priorities for United States negotiators.

That law requires U.S. negotiators to ask for accelerated implementation of TRIPS and mandates that any multilateral or bilateral trade agreement entered into by the United States “reflect a standard of protection similar to that found in United States law.” At the same time, negotiators were told to respect the Doha Declaration.

What’s more, some of the flexibilities built into TRIPS to assuage poor-country concerns are problematic. In principle, they allow countries to issue licenses for the production and sale of generic versions of patented drugs to address public health problems. But, as the case of South Africa shows, the system is a tangle.

For its own political reasons, South Africa’s health ministry refused to issue compulsory licenses for the sale of generic antiretrovirals for AIDS treatment. But in October, the country’s Competition Commission took an indirect route to getting generics into use, attacking the monopoly inherent in patent rights by upholding a claim that patentees had engaged in excessive pricing. This ruling elicited the licensing offer by Glaxo-SmithKline and Boehringer Ingelheim, noted above, as an out-of-court settlement.

South Africa will thus get antiretrovirals at well below the price charged in rich countries. But it took years of focused campaigning,



There are, after all, many barriers to drug access in poor countries ranging from income to transportation to health care infrastructure, and it may seem a distraction to continue arguing over protection of intellectual property rights.

persistent media attention, and legal and regulatory wrangling to get there. This process can hardly serve as a template for resolving the tensions inherent in property rights in most pharmaceuticals. Because patents are national in scope – there is no such thing as a global patent – a generics firm hoping to achieve economies of scale in production by supplying a group of, say, 20 poor countries

would need to obtain a license on relevant patents in each of those countries as well as at home.

To take another example, consider the international agreement last August in Cancun that allows firms to produce pharmaceuticals for export under compulsory license in cases where recipient countries cannot produce their own. The deal was greeted with

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relief after nine months of diplomatic deadlock. However, its terms include a remarkable list of conditions on all parties trying to follow the letter of the agreement – conditions that are likely to make it unworkable in practice.

What's more, the terms of the August agreement are so vague – as are the procedures and timing for complaints by patent-holders – that uncertainty will make exporters of generics reluctant to enter foreign markets. The Canadian prime minister has declared that Canada will take a first step toward implementing the agreement by allowing its manufacturers to respond to export requests. But the proposed Canadian legislation enabling generic drug exports adds yet further restrictions to those imposed by the August WTO agreement.

The Canadians would, for example, limit coverage to a defined set of eligible pharmaceuticals. The WTO agreement does not require that. The proposed Canadian legislation would also give patentholders a chance to match the price offered by any generic manufacturer, and thereby forestall issuance of a license. This reduces the incentive for generics makers to bid to enter markets in the first place.

HOW DID WE GET HERE?

Most people recognize both the value of the contributions to global health that have come from private pharmaceutical research and the fact that the patent system plays a pivotal role in supporting that research. By the same token, most recognize that markets in the poorest countries are not a significant part of this incentive equation. But it has proven very difficult to draw lines separating the markets that matter from the perspective of innovation incentives and those that do not – and to do it in a way that is both clear and reason-

able. “Everyone agrees we should do something for the very poorest countries,” Daniel Vasella, the chief executive of Novartis, acknowledged. “But if we expand that to cover all countries other than the richest and to cover all diseases, that will completely undermine intellectual property.”

Confronted with a situation in which it is hard to draw lines, the industry has understandably tried to obtain the strongest protections possible using whatever means were available. Inevitably, they have overreached, provoking the ire of economic development activists, poor-country governments and public opinion at home.

There is a way to resolve the dilemma – a way to create a mechanism for defining and implementing a more rational structure of global protection. It would give the fullest protection where research incentives are currently weak (e.g., drugs for malaria), while at the same time facilitating competition from generic drugs in poorer countries for treating diseases like cancer and heart disease, where developed-country markets already provide strong research incentives. What's more, the mechanism would evolve automatically in response to the economic maturity of countries and changes in market opportunities.

THE FOREIGN-FILING LICENSE SOLUTION

The proposed mechanism involves a straightforward change in legislation in rich countries and – in the rare cases where it might require enforcement – uses existing infrastructure in those countries only. It imposes no regulatory burden on developing countries.

Under the plan, some countries would be allowed access to generics immediately, but only as long as their markets represent a very small portion of global demand – say, no more than 2 percent of sales in the aggregate. Which countries qualified would depend on



income level – the poorest would benefit the most – and on the disease.

For example, drugs aimed at malaria would be protected in most countries, because the low-income countries are a more significant share of the market. Drugs to treat, say, high blood pressure, prostate cancer or acid-reflux disease are mostly sold in the rich countries, so many poor countries could be open to generics. For countries above some average income threshold – perhaps \$5,000 a year – all patented drugs would receive full protection, regardless of demand.

Arguably, the most important part of the plan is how little it asks of developing-country governments. They do not need to change

Even a modest shift in priorities in response to the modest increase in developing country demand for new drugs would represent a significant gain.

their patent laws or enforcement procedures, or make complex decisions about compulsory licensing. Although the regulatory approach

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is aimed at changing access to drugs in poor countries, it would not require them to regulate anything. In fact, their obligations under TRIPS would stay just as they are now.

The mechanism is exceedingly simple. Take the example of a drug that has been invented in the United States and is freshly patented. Under current U.S. regulations, the owner of the patent is obligated to obtain permission from Washington before it can apply for parallel patent protection in other countries (the foreign filing license). The proposal would simply require the patent holder to sign a declaration in order to obtain this permission – a declaration that the permission being sought would not be used to restrict the sale of the drug in poor countries with minimal demand. If the patent owner later reneged by pressing its patent claims against competitors in a proscribed market, it would put at risk its right to enforce the patent in the United States, where it really mattered.

Adjustments in coverage would follow automatically from changes in market conditions. So, for example, India would be allowed easy access to generics initially, but the country would grow into patent protection as its economy blossomed. This extension in protection would not require the Indian government to change its laws or to invest additional resources in policing patents. All of the institutions required to implement and operate the system are already in place in the rich countries.

Note that the approach does not limit protection for intellectual property actually created in low-income countries; nor does it

undermine incentives to invest in home-grown R&D. The policy would apply only to inventions in high-income countries; inventors in poor countries would continue to enjoy whatever protection is offered by their own governments. To put it another way, it would give local inventors a chance to develop an appreciation of the patent system, and would give governments an incentive to build



the enforcement capability necessary for a patent system to really work.

Note, too, that the plan avoids the objectionable process of designating countries as part of the very-poor group. The only income-based dividing line would be between countries with incomes above \$5,000 per capita and those below. And since the approach would not alter the text of the TRIPS agreement, existing flexibility in TRIPS would remain to address public health concerns in countries falling outside the scope of the policy.

In sum, both existing rights and obligations would remain in place. Companies would simply forego exercising their rights in the poorest countries, thereby removing the major area of disagreement.

DIFFERENT DISEASES, DIFFERENT MARKETS

The key to the proposal is, of course, the real-

ity that pharmaceutical markets are extremely different, depending on the disease that is treated. Consider truly global diseases first – those that are prevalent worldwide. Global diseases impose an enormous health cost on poor countries. HIV/AIDS is the first that comes to mind, but there are many others. For example, the World Health Organization estimates that the health burden in poor countries from two global diseases, cancer

Would enforcing strong patent rights in developing countries further the research effort on diseases that bedevil these countries? Incentives to invest are weak not only because of limited patent protection in the developing world, but also because people there are poor. In 1998, 17 countries spent no more than \$10 per person annually on all health expenditures. But it is equally clear that current policies have largely failed to

The plan gives local inventors a chance to develop an appreciation of the patent system, and gives governments an incentive to build the enforcement capability necessary for a patent system to really work.

and heart disease, is four times the burden on those countries due to malaria. Yet the incentives for industry to develop drugs to treat such diseases lie almost exclusively in demand from affluent economies. To take one example, countries with about one half of the world's population contribute less than 2 percent to spending on cardiovascular drugs.

On the other end of the spectrum, there is an urgent need for more investment in diseases that primarily affect poor countries. In 2001, two million children died from malaria, but spending on malaria research represents less than one-half of 1 percent of the total investment in drug R&D globally. It should be no surprise, then, that only 8 of 1,233 drugs licensed by the United States Food and Drug Administration from 1975 to 1997 were developed specifically for tropical diseases in humans. If there is to be a market for drugs treating these diseases, much of it must lie in low-income countries.

generate products for the particular health needs of the world's poor.

The prospect of strong patent rights in poor countries world would not cause industry to reorient its research priorities toward developing-countries' needs. But global private-sector R&D in pharmaceuticals is enormous – \$32 billion in 2002 – and it continues to grow. So even a modest shift in priorities in response to the modest increase in poor-country demand for new drugs would represent a significant gain.

PIE IN THE SKY OR COMMON SENSE?

Although the fight over defining the scope of patent rights for drugs is proving extremely persistent and difficult to settle, it does not stem from inherently conflicting goals. The pharmaceutical industry wants, above all, to protect its rights in rich economies, and it would like to see effective protection evolve in poorer countries as they grow into more

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attractive markets. Making profits in the low-income countries is simply not an industry objective.

For their part, the economic development community is primarily concerned with keeping drug prices low in the poorest countries. These are not opposing objectives.

This proposal offers a fix that respects the underlying logic of the patent system. The right lines can be drawn in the trade-off between prices and investment incentives because different lines can be drawn for different products.

The mechanics of implementing this proposal are straightforward. The industry must decide that a virtually costless compromise on a more acceptable patent system is a whole lot better than trench warfare over drug access in low-income countries. There remain divergent views within and between organizations on this point. Those who have been most involved in the debate would have to be convinced that the solution described here does not create dangerous precedents. And this would require some thinking outside the box.

If consensus can be reached, the governments of countries with research-based pharmaceutical sectors would probably want to

coordinate the implementation – though it could be done unilaterally. This group includes the United States, Canada, the European community and Japan. Each country would revise its patent code to add a foreign filing license provision (if one is not already there), with the requirement to sign the declaration and other details.

The approach would plainly not solve every problem associated with disparities in access to lifesaving drugs. Moreover, controversy over the strength of patent rights would continue with respect to countries above the income cutoff. There might still be an argument, for example, over whether Eastern European transition states should be held to different standards than the richest countries. What the policy would do is provide a simple way to remove the poorest countries from the patent debate, so that their access to new pharmaceuticals would not be needlessly complicated by rules made to protect other markets.

Some analysts have suggested that efforts to define such a middle ground on drug patent protection are hopeless because both sides have dug in. But compromise is happening in an ad hoc fashion in the context of specific disputes. This proposal offers a fix that respects the underlying logic of the patent system.

The right lines can be drawn in the trade-off between prices and investment incentives because different lines can be drawn for different products. The proposal asks pharmaceutical companies to take a more defensible position on global patents, but one that protects their significant markets. It asks lower-income countries to give private enterprise meaningful patent rights where those rights can possibly contribute to innovation.

Sometimes, it seems, free lunches really can be almost free.



Mark B. McClellan, Commissioner of the Food and Drug Administration, is arguably the most qualified person ever appointed to the post. Along with a medical degree from Harvard he holds a doctorate in economics from MIT, and was a prolific researcher on the economics of health care at Stanford before taking his current post. Oh, yes – did I mention that Dr. McClellan is very well connected in Washington and Texas? He was a senior Treasury official in the Clinton Administration and stayed on to become a member of the President's Council of Economic Advisers for Dubya. His brother Scott is now the White House press secretary and his mother, Carole Keeton Strayhorn, is the Texas State Comptroller as well as one of the most popular Republican politicians in the state.

McClellan's September 2003 speech before the First International Colloquium on Generic Medicine in Cancun is notable because it explores a central issue facing the drug industry and its regula-



tors: How should the enormous R&D costs of new pharmaceuticals be apportioned among the world's consumers? Here, we offer excerpts from the speech, along with commentary by Iain Cockburn, a distinguished economic researcher at Boston University who specializes in health care issues.

— Peter Passell

It is no accident

that my first international speech concerns the topic of improving the development and availability of affordable and safe medicines.... When it comes to affordable, safe and innovative medicines, we are facing a global crisis today. This crisis will get worse if we do not take more steps now to start working together to address it.

And so that is my main challenge to all of you here today. If we are all going to enjoy the great benefits that lie ahead in this century from improvements in medical treatments, we need to work together to find better ways to solve the global problem of how we are going to pay for them. Prescription medicines, drugs and biologics are truly global products today. They can and should benefit all of the people of the world. And so we need a global strategy to get the most benefits from innovative medical treatments for all of the people of the world....

New drugs allow children with rheumatoid arthritis to walk and to go to school. New drugs shrink cancerous tumors and they control the advance of HIV. They prevent or halt heart disease, slow the progression of multiple sclerosis, and cure infectious diseases.

New drugs often reduce overall health costs. For diseases such as ulcers, a few pills have replaced major surgery. New drugs also shorten hospitalizations and prevent the costly complications of chronic diseases such as diabetes and high blood pressure. New drugs have been a special blessing to seniors, who are better able to overcome many diseases to live longer and better lives.

In fact, over the last century, the value of gains in life expectancy seen in the U.S. is greater than the total value of all the measured growth in our economic output. New drugs are no small part of this medical mira-

cle. The reduction in U.S. mortality from cardiovascular disease alone has been valued at \$1.5 trillion annually from 1970 to 1990. And for the developing countries of the world, the health improvements have been even more valuable. Drug treatments for infectious diseases and other illnesses of the developing world have permitted even greater gains in life expectancy in developing nations than in countries like the U.S. Consequently, innovation in drugs and other medical treatments is helping to reduce the worldwide economic inequality that has long resulted from health inequality.

And the promise for the future is even greater. We're at a stage of scientific progress when a large range of new technologies, such as genomics and proteomics, are becoming widely used in the development of new treatments, and these new sciences just might bring about new breakthroughs. Many new drugs currently in clinical trials are no longer scattershot one-size-fits-all treatments, but carefully targeted to be highly effective given the molecular features of a disease in a particular type of patient. These same new sciences also hold promise for making the process for developing new medical technologies faster and more predictable....

Unfortunately, though, developing new medicines is generally pretty hard work, and it's increasingly expensive and uncertain. According to some estimates, a new drug costs more than \$800 million to develop, and while that exact number has been disputed, none have argued with the fact that the cost of development is large and has doubled over the past decade. And it's an uncertain process. For every 5,000 to 10,000 compounds screened for development, 250 proceed to preclinical testing, only five enter clinical testing and only one results in an application to FDA. And fewer than one in two that even

enter the most expensive phase of clinical testing, so-called Phase 3, actually result in applications to FDA. That's a costly bet with very long odds – and the only payback to a product developer comes at the end, after all this money is spent, if the drug actually works.

With all of the promising recent developments in biomedical research, I can think of no better use for some of our brightest talents

holding a patent for a new and innovative product does not mean that its value to world health can be recovered, that means less development of new treatments and less improvement in world health.

If we do not find better ways to share the burden of developing new drugs and biologics, all of us will suffer. The benefits of these treatments are global, and so if we think only of the short-term interest of our own coun-

The reduction in U.S. mortality from cardiovascular disease alone has been valued at \$1.5 trillion annually from 1970 to 1990.

and a significant part of our collective resources than to turn these scientific insights into safe and effective new treatments. But without an assurance of payment for success that reflects the value of these new treatments to the world, the developers of new medical products will not do it. They will not risk the high cost and the years of effort in collaboration across an increasingly broad range of scientific disciplines.

As nations are working hard to find ways to tighten price regulations and shift costs elsewhere, we run a serious risk if product developers don't think they can get a fair payment when they succeed. They'll stop trying. They'll turn to products where the prices aren't regulated, like erectile dysfunction drugs and other lifestyle drugs. Or they'll turn away from developing new products altogether. We've seen this problem in new treatments for the agents of bioterrorism. There is no natural "market," so product developers have to depend on whatever governments are willing to pay. And as a result, the treatments available to prevent bioterrorist diseases, like smallpox, haven't really changed in decades. If

try, we all lose the opportunity for a healthier world. The heart of this problem is that we are not all paying our fair share of the costs of bringing new treatments to the world. And this problem is getting worse.

Our governments need to start by sharing the burden of the increasingly complex basic science that goes into the development of new drugs and biologics. In the United States, we've responded to the new opportunities that exist in the lab, by doubling our NIH [National Institutes of Health] budget to over \$27 billion. As a share of GDP, this is about four times as much as European Union countries spend. But on an interconnected planet, all of this spending turns into biomedical knowledge that is transmitted worldwide for the good of public health worldwide. If other developed countries contributed to this worldwide effort in proportion to their GDP, we would build the foundations for better treatments much faster.

Efforts to fund discoveries in basic science and biomedical "proof of concept" for a potential new medicine are critically important. But every day in our work at FDA, we see

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that such efforts are not enough to actually produce drugs that are reliably safe and effective for patients. In fact, more than 75 percent of licensed inventions discovered by NIH-funded researchers were no more than a proof of concept, a long way from reliable products.

Government grants cannot solve all of the problems of drug absorption and kinetics, interactions, toxicities, manufacturing concerns and countless other issues. There are just too many such problems, and solving them is more an art than a science today. That's why so many promising new treatments that sound good when tested in mice never succeed in humans. This is especially true for the increasing number of biologic drugs, which are much larger and more complex than traditional drugs, and which present unique and complex issues in determining their safety and effectiveness.

If we want to continue to enjoy the global benefits of these new products, we need to all consider the global problem of how we pay for them. Prescription drugs are truly global products today, and we need a global strategy to get the most benefit from new medications for all of the people of the world.

We are partly there. Industrialized nations are increasingly coming to the conclusion that, in general, protecting patents is vital for health. Even though violating patents on, say, new software or electronics might lead to lower prices in the short term, countries understand that the result is fewer innovative products and less economic development. But in contrast to many other products that are increasingly available globally, prescription drugs are different in that the value of holding these patents is limited by increasingly strict government price controls in most countries. In many ways, the economic consequences of overly strict price controls on

drugs are no different than violating the patent directly through compulsory licensing to make copies of the drug. Either way, there isn't likely to be a fair payment based on the value of the new patented product.

This year, Americans, who account for a [small] fraction of prescription drug use worldwide, will pay for about half of all pharmaceutical spending worldwide. By contrast, citizens in the world's third-largest economy, Germany, paid less than 5 percent. The same kind of drug payment disparity is true for many other developed nations, who have about as much ability to pay as Americans do. Yet on the whole, people in these other nations are getting most of the same kinds of drugs and the many of the same kinds of health benefits as Americans. And it's not only Americans that seem to be paying an unfair share. Drug prices on average are significantly higher in countries like Poland than they are in France and Germany – even though people in those countries have significantly less economic wealth than the countries of Western Europe.

Why does this happen?

After the usually long and extensive development process to show that a drug is safe and effective, all of the R&D costs have been spent. All that's left are the production costs of making and distributing the medicines themselves. But the remaining production costs only account for about 25 to 50 percent of the total cost of developing and providing a new medicine for a particular country. Obviously, each country would like to pay only this additional cost to obtain the drug for the additional patients in that country. Nobody wants to pay for all the rest of the costs – all the money that has already been

spent researching and developing a new medicine and researching and developing its production and labeling.

And some of the world's richest nations are driving the world's hardest bargains. In fact, many developed countries are in effect banding together to get the same price. For example, many high-income countries regulate their prices by setting them equal to those in other countries that already have rigid

lot, and leads the world.

But it's important to look at the facts. A large amount of research, which we reviewed at an expert conference earlier this week, seems to show that on net such advertising benefits the public health. It gets more people into treatment for conditions that are under-treated in the population. Advertising clearly needs to be regulated, so that consumers and doctors get an accurate picture of the key

Americans pay for about half of all pharmaceutical spending worldwide. Citizens in the world's third-largest economy, Germany, paid less than 5 percent.

price controls. This system is used in Canada, informally in Japan, and in some countries in Europe. By linking together, they may get even more power to only pay for the cost of making additional pills. As a result, many relatively wealthy countries are moving away from covering any significant part of the costs of research and development. They are leaving development costs for nations with less ability or will to extract lower prices.

But unless someone covers the cost of R&D investment, which accounts for 20 percent or more of the revenue from pharmaceuticals, that investment will slow or stop, and so will the improvements in health that we've become used to seeing in recent decades.

The United States is now covering most of these costs of developing a new drug to the point where it can be used by the population of the world. Some have argued – I think incorrectly – that other factors account for higher prices in the U.S. That the U.S. basically deserves its higher prices. One reason, they say, is American drug advertising. Direct-to-consumer advertising in the U.S. has grown a

risks and benefits of a treatment – and we are taking new steps, including developing some new regulatory guidance on how to communicate risk and benefit information to consumers.

But although the ads are highly visible, they account for less than 2 percent of U.S. pharmaceutical spending, and so they can't be a key driver of drug costs. In fact, the largest part of the marketing costs in the U.S. (about \$10 billion) are free samples of drugs, which enable patients to find out if a drug works for them without having to pay for it. That seems like a good way to help patients learn about drugs cheaply.

People have also argued that the higher U.S. costs are for more spending on "me-too" drugs. I know there is a lot of anger because the drug companies are perceived by some as popularizing drugs that are only slightly different and that may offer only marginal benefits over cheaper alternatives. Some of those criticisms are unfair, since many such drugs do provide subtle but important benefits, like fewer side effects or a better dosing schedule. And having multiple drugs in a class means

that drug buyers can benefit from more competition. But the fact is that “me-too” drugs are not a large part of R&D spending. Over the 1990s, for example, only about 20 percent of pharmaceutical R&D spending was devoted to improving or modifying existing products.

The highest prices in the world are now paid by Americans on fixed incomes who have little ability to pay and great needs.

Many around the world also believe that U.S. drug prices are higher because our liability system is much more costly. They argue that our liability system encourages lawsuits based on bad outcomes not negligent treatments, and that product developers often incur large payouts in such suits, many of which are of dubious scientific merit.

It is true that our liability system does add significantly to costs compared to other nations, and there are good ideas under consideration in the U.S. on how we can do a better job of making our liability system work more efficiently in compensating those who are injured.

All of these additional costs, many of which are important, cannot account for all of the higher prices that people in the U.S. actually pay. The truth is that the main reason prices are higher is that our country is paying the bulk of the costs of developing new treatments. That’s got many Americans angry. The highest prices in the world are now paid by

some Americans – seniors on fixed incomes – who have little ability to pay and great needs. I hope we will fix this soon by getting them an overdue Medicare drug benefit. But we also need to do more to address the issue of sharing the global burden of developing new treatments.

This is a real public health problem. The difference in payments for drugs is now translating into differences in spending going into drug R&D, as the price controls discourage the R&D needed to develop new products. In 1990, European pharmaceutical firms spent 75 percent more on R&D than American firms. By 2000, American firms spent over a third more than European firms. Even firms that are technically European are moving their most essential operations to the United States.

And the impact of excessive price controls on R&D is translating into an impact on the development of new products. American manufacturers now account for eight of the top 10 worldwide best-selling medicines. And recent studies show that, on average, new medicines reach patients months earlier in the United States than in Europe. Even as Americans are going the other way to get lower prices on some drugs, Canadians have had to cross the border to the United States to get access to new breakthrough medicines, like Gleevec, that are not available in Canada in a timely or easy way.

Reducing the needed incentives to develop new medicines through excessive price controls is slowing the process of drug development worldwide. If we continue on our current path of trying harder and harder to shift the costs of developing new medicines to someone else, rather than paying our fair share, everyone’s effort to get a free ride on new drugs will grind the global development of new drugs to a halt.

That's unfair and unjust.

It's unfair to Americans, who are bearing an increasing share of the burden, and cannot be expected to do so indefinitely. But it's also unfair to the citizens of the rest of the world too. At FDA, my job is to help protect and advance the health of Americans. And I see the current situation as a real threat to advancing our health. The price differences are creating pressures for the importation of unapproved drugs, including drugs offered over the Internet or from untrained storefront operators that promise equivalence to FDA-approved drugs, but are not approved, cannot be effectively regulated under current law by us or other nations, and frequently turn out to be manufactured, shipped, stored or labeled in ways that make them unsafe.

And high prices are putting some of the most valuable new medicines beyond the means of many Americans. Americans are being forced to choose between regulated drugs that are safe, and "buyer beware" drugs that are affordable. I don't think Americans or anyone in the world should have to settle for that choice, and we are all working hard on better solutions – including regulatory changes at FDA as well as legislative changes, like new prescription drug coverage, in Congress. We also need to think together about new solutions internationally. A lot of people view drug pricing as an either-or choice: Either each country can try its best to get the lowest prices for itself and shift the costs elsewhere, and we may as well do this since everyone else does, because if everyone else does it, there's no way to support the development of more valuable new drugs anyway. Or, we can try to encourage very costly drug innovation. But as drug costs keep ris-

ing, that seems impossible for any nation to afford.

I don't agree with this either-or choice. If we work together, we can bring down the costs of developing new drugs, and we can share those costs in a way that's manageable for all of the countries that benefit from them.

At FDA, we are taking a number of other steps to try to reduce the high cost of developing medications, both new medications and legitimate generics. We want to partner with all of your countries in this effort. A key element of our new planning is what we call "efficient risk management." In all of our major policies and regulations, we're seeking to use the best biomedical science, the best risk-management science, and the best economic science to achieve our health policy goals as efficiently as possible.

We are trying to make the process for developing new technology less costly, without sacrificing our high standards. We need to make the development process less risky, with greater predictability and less time from concept to bedside. We are also modernizing the way we regulate prescription drug manufacturing, to encourage companies to develop the same kinds of continuous improvement techniques that have reduced costs and improved quality enormously in other high-tech industries like semiconductors.

And we are working on improved data reporting systems from electronic medical records, and on a new electronic product label – so that patients and doctors can get up-to-date information about a drug's risks and benefits in order to make smart decisions. If we do a better job of arming consumers and their doctors with better information, we can avoid costly prescriptions that are inappropriate or unnecessary.

In all of these areas, we are working with

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international regulatory processes and our counterpart agencies in other nations. If we can harmonize our regulations based on the best and latest science, and the best ideas from around the world, I am confident that we can substantially reduce the cost and uncertainty of developing and using new medicines....

Our efforts to work together – in order to harmonize regulations for developing and manufacturing drugs – can have an enormous impact on their cost. And steps, such as improving access to generic drugs after patents expire, and to develop and share better information on the risks and benefits of drugs, can reduce the cost of using medications substantially. But even so, the fact remains that developing new medicines is costly and uncertain. That means we also need to work together to support the cost of research and development if we all want to continue to share in the benefits of medical progress.

With more promising new treatments in the pipeline than ever, I don't believe the billions of people around the world who are suffering today from diseases that may be treatable in the near future can wait. It is time for developed nations, recognizing their shared interest in bringing better treatments to market, to work together to find ways to fairly share the costs – not just the benefits – of new drugs.

I don't have all the answers, but I think it's time to start the international discussion. For example, one way might be to aim for worldwide drug prices in proportion to a nation's income. It seems fair that the average price of a new treatment ought to bear some relation to a nation's income. Developing nations should pay little; rich nations would pay more to support the research and development. If all of the developed countries share this bur-

den together, none need be stuck with very high prices.

I'm very encouraged by some first steps in this direction. For example, a recent Doha trade agreement will make available low-cost medications to treat the infectious diseases that are burdening developing countries with little ability to pay.

This first-ever international arrangement not only paved the way for greater access to low-cost, up-to-date drugs in developing countries that cannot afford them and really need them, it also required the developed nations of the world to make new promises to avoid re-importation and compulsory licensing, so as not to take advantage of the low prices for peoples who cannot pay.

This is an important first step, but we need to do more. I'm also encouraged that some prominent health officials in Europe are once again talking about the corrosive effects of excessive price regulations. It is time for everyone to take this challenge up for real. This goes for drug and biologic companies too: if they don't want countries acting in their own short-term interest with price controls, then they too need to work harder to get prices that share the burden fairly, rather than simply putting the greatest burden on those people who are least able to protect themselves against higher prices....

I know that many are complacent with the current situation, in which the United States has borne the bulk of costs. I know it is not clear how to work together internationally to create better ways to share the burden than are provided by our current trade agreements. But it is clear to me that we cannot carry the lion's share of this burden for much longer. And the consequences for world health will be grave. If we don't come up with a better alternative, then each nation only acts with its own short-term interest in mind. ☐

Iain Cockburn

Mark McClellan is surely right that mechanisms for rewarding drug makers are both unfair because some Americans pay more than their share, and inefficient because the patchwork of national price regulations threatens to retard innovation in life-extending and life-enhancing pharmaceuticals. But righting the inequities and inefficiencies will not be easy. Indeed, current trends suggest that the problems are growing worse.

As the political pressure to permit re-imports of drugs from Canada illustrates, cross-border variation in prices seems likely to force significant changes in the international pharmaceutical marketplace. If advocates for lower prices get their way, changes in the U.S. market will drive the prices of many drugs toward an international norm, whether through the mechanism of re-importation, through explicit price regulation or through de facto price regulation via greater government participation in purchasing.

In the near term, some groups of domestic buyers in the United States, including some of the most economically disadvantaged, will likely see significant savings. In the long run, however, these benefits will surely be limited. What's more, the international convergence of prices would potentially carry with it some very serious costs for all consumers of pharmaceuticals, with the world's poorest people bearing the brunt.

Unless the international community is also willing to abandon patent protection for pharmaceuticals, undermining drug compa-

nies' capacity to discriminate among groups of consumers according to their ability to pay would mean that low-income countries would either pay higher prices or face chronic shortages of vital medicines. Moreover, if drug companies lost the ability to realize premium prices in their largest market (the United States), and were effectively left to negotiate prices with national health agencies and regulators everywhere, they would likely scale back investment and redirect R&D toward "safer" projects.

ARE DRUGS REALLY CHEAPER IN CANADA?

Public attention in the United States has been focused on differences between U.S. and Canadian prices of drugs, with news reports leaving the impression that U.S. prices are typically 50 percent to 100 percent higher. But such comparisons are misleading.

Many studies of international pricing differences have been flawed by a failure to make apples-to-apples comparisons. Yes, there are startlingly wide gaps between prices paid by

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uninsured consumers for on-patent branded drugs in mom-and-pop pharmacies in the United States and the prices paid for generic versions of the same drugs in Canadian stores and mail-order houses. But such differences apply within countries as well as between them. Within the United States, for example, drug prices vary dramatically according to the type of retailer and whether an insurance group has negotiated a price on behalf of the consumer.

Efforts to compare prices across countries using representative baskets of products and wholesale “factory gate” prices have been frustrated by difficulties in obtaining data on variations in drug use patterns, or on actual prices paid net of discounts – not to mention arcane methodological difficulties inherent in constructing and interpreting any price index. Most egregious from an economic perspective, comparisons have typically used currency exchange rates rather than conversions into common currency that reflect international differences in incomes and purchasing power.

Notwithstanding these concerns, it is clear that uninsured cash payers in the United States do face some of the world’s highest “sticker” prices for pharmaceuticals. Other U.S. purchasers may do much better on an apples-to-apples basis. But the price differences are real, and are clearly visible in statistics on aggregate national spending on pharmaceuticals.

Legislation to permit re-importation of drugs appears to be the favored policy tool of advocates for lower U.S. drug prices. But what would happen if the legal impediments to cross-border trade in pharmaceuticals were eliminated? The impact would almost certainly vary from drug to drug because the factors determining pricing differences vary so

much. As is the case for other traded goods, the effects are also likely to be quite sensitive to movements in currency exchange rates as well as the speed at which supply and demand changes are passed through the distribution chain.

Most important, though, would be the responses of foreign governments and drug manufacturers. Consider the case of Canada and the United States. If Ottawa stood by passively, and manufacturers were willing to supply much larger amounts of their products to Canadian distributors, price differences in the two markets would narrow. For patented drugs, where the patent holder sets prices, Americans would pay less and Canadians more.

But Canadian government agencies are highly unlikely to stand by while drug exports to the United States drive up Canadian prices. Canada has a price regulator charged with limiting price increases on most patented drugs to the rate of change of the overall consumer price index. If prices were not allowed to rise, one would expect chronic shortages of patented drugs in Canada as distributors and retailers diverted supply to the higher priced market. And this, in turn, would lead to pressure to eliminate patent protection in Canada, or import large quantities of drugs from elsewhere in the world – thereby “passing the buck” of higher prices to the lower-income countries.

By the same token, manufacturers surely would be uncooperative. Indeed, some have already acted to limit supply of their products to arbitrage-oriented sellers in Canada. If the effects of trade on U.S. prices were sufficiently large, manufacturers might decide to stop selling existing products or to not launch new products in Canada. Again, Canadian consumers would be the victims, and some counteraction by Canadian agencies would be like-

ly. At the very least, we should anticipate manufacturers taking socially wasteful steps to maintain market segmentation – for example, by devising “just different enough” variations of the same drug to sell in different countries using different brand names, etc.

The most obvious “solution” for Canada is, of course, to weaken or remove patent protection by requiring compulsory licensing that generates generic equivalents. This would leave the United States in the position

particularly by lower-income countries that would be likely to interpret the U.S. position as “can pay, won’t pay.”

Widespread abandonment of the patent system is highly unlikely. Nor is the United States likely to adopt a system of explicit price controls. But removing barriers to cross-border trade might start a slide down a slippery slope, leading to significantly lower average prices worldwide, weakened intellectual property protection, and a markedly less

The most obvious “solution” for Canada is, of course, to weaken patent protection – for example, by requiring compulsory licensing.

of either following suit or stopping imports of patent-protected drugs.

These economic pressures point toward some worrying outcomes. If the United States tries to bring its prices closer to the world average through re-importation, manufacturers would have to be coerced into supplying sufficient volume to low-price countries to allow re-importation as well as meeting these countries’ needs. This would most likely be done by threats to revoke or weaken patents, with severe effects on future innovation.

If world supply were not increased, upward pressure on prices outside the U.S. would likely provoke a regulatory “rush to the bottom” with other high-income countries intensifying their use of price regulation and government procurement policy to prevent their prices rising toward a uniform world price as the U.S. price fell. The alternative would be for the United States to force down domestic prices through price controls, which would not only reduce R&D, but also prompt retaliatory rounds of price cuts abroad – par-

attractive business environment for pharma. The short-term benefits from lower prices would come at the cost of weakened incentives for innovation. Equally dismaying, the limited progress that has been made toward lowering prices and increasing access to medicines in the very poorest countries would likely be reversed.

THE IMPACT OF LOWERING THE U.S. PRICE ON R&D

Worldwide R&D spending by pharmaceutical companies totaled more than \$50 billion in 2002. In recent years investment has accelerated dramatically as the industry has responded both to new scientific opportunities, and to a changing division of labor in biomedical research among publicly funded institutions, big pharma and new biotechnology companies. Although these increases in R&D spending have been accompanied by an apparent slowdown in the rate at which new drugs have been approved, we can anticipate very substantial future payoffs down the line.

COCKBURN

Alarmingly, however, the commercial justification for these large and growing levels of expenditure is beginning to look shaky. New technologies such as ultra-high-throughput screening, microfluidics, bioinformatics and combinatorial chemistry, combined with major advances in the fundamental science base of the industry, hold out the promise of faster and better drug discovery, and the prospect of safe and effective treatments for costly disorders, including arterial disease, diabetes, obesity, Alzheimer's, Parkinson's and schizophrenia.

But developing drugs and bringing them to market remains an extraordinarily risky proposition. Blockbuster drugs are hugely profitable but rare, and are the result of investors' willingness to support years of investment in costly research programs with highly uncertain outcomes. Without the premium prices, and the resulting high rates of return realized by "winners" in this high-stakes game, current levels of R&D expenditure are probably unsustainable.

To date, the industry has relied on sales in the U.S. market, which is very large and generally free of price regulation, to support its investment. Here, the legal system has supported patent protection of pharmaceuticals. And consumers have collectively expressed a high willingness to pay for health care, as evidenced by the share of GDP devoted to health care. In contrast, other markets have proven less attractive, and less profitable, for the industry.

Most of the other wealthy countries have some form of price regulation, combined with centralized purchasing, restrictive reimbursement rules and reference-based pricing schemes. Some, such as Canada and Italy, have experimented with compulsory licensing or other ways to void or weaken patent

rights. These policies have been quite effective in limiting growth in expenditures on pharmaceuticals. Outside the rich countries a combination of low incomes, limited health care infrastructure, risky business environments and nonexistent intellectual property protection have made billions of people largely economically irrelevant to the industry.

If political pressure to reduce prices in the United States, whether through re-imports or price regulation, actually results in worldwide convergence of prices toward European and Canadian levels, incentives for R&D will be substantially weakened. Quantifying the potential impact on R&D expenditures is difficult. One back-of-the-envelope study by the Canadian-based Fraser Institute suggests that, in a worst-case scenario, global R&D could drop by as much as 50 percent if Canadian prices applied to the U.S. market. Even with less aggressive assumptions, global R&D spending could fall by 10 percent to 20 percent if sales and prices drop significantly in the United States.

SHARING THE BURDEN?

Other wealthy countries are free-riding on Americans' willingness to maintain R&D incentives by paying premium prices. And FDA Commissioner Mark McClellan, among others, suggests that some structure needs to be put into place to "share the burden." Though this notion is politically appealing (in the United States), there are some huge obstacles to overcome.

First, it is far from clear what such a structure might be. In theory, the optimal solution to the problem of financing global pharmaceutical R&D is straightforward. Economists have long understood that a monopolist (in this case, think patent holder) incurring fixed costs to serve multiple markets will maximize profits by setting prices in each market ac-

cording to local demand conditions. Society's interests can be maximized in this situation by lowering monopoly prices proportionately across the board to the point at which the monopolist covers its fixed costs – in this case, R&D – and earns a normal profit.

But even if countries could agree on such transnational price regulation, the regulator would face some very difficult practical issues. Patented drugs can't be described as

On the demand side, sensitivity to price changes can be difficult to estimate where insurers, hospitals and physicians referee consumption decisions, and where insurance and government subsidies insulate end users from "real" prices. But perhaps the greatest operational challenge for a regulator operating such a scheme would be determining the "normal" rate of return required to induce socially desirable levels of investment in R&D.

Without premium prices, and the resulting high rates of return realized by "winners" in this high-stakes game, current levels of R&D expenditure are probably unsustainable.

simple monopolies. Thus the price regulator would have to factor in all sorts of variables ranging from the availability of substitute drugs, the introduction of new products, the finite life of patents, and the entry and exit of manufacturers. Marginal costs are difficult to measure in even very simple circumstances. Here, they would have to include not just manufacturing costs, but costs of distribution and marketing. Some share of pharmaceutical marketing activity is socially valuable in that it provides information to patients and physicians, while "persuasive" winter conferences for physicians in sunny places with convenient golf courses, and "lifestyle" advertising to consumers, would presumably not be considered.

But drawing such distinctions in practice is far from straightforward. Moreover, legal and social institutions in different countries also impose idiosyncratic costs. For example, variation in costs associated with product liability claims have been identified as one component of international price differences.

Inferring this from past experience would be a hazardous exercise. The high level of risk associated with pharmaceutical R&D has resulted in wide variation in industry profits over time, and very significant differences in the profitability of individual drug makers. As weak (or unlucky) firms have disappeared, a powerful "survivorship bias" has rendered after-the-fact returns a very poor signal of the anticipated profitability of developing new drugs – which is what drives investment in R&D. Most worryingly, the long lags between investment decisions and outcomes, and the significant role of externalities, such as knowledge spillovers among firms and between public and private sectors, have made it very difficult to calculate rates of return on R&D – or to be confident about the response of firms to expectations about future profitability.

Adding an international dimension raises further difficulties. How would a transnational regulator coexist with national policymakers with varying priorities? Any kind of international price regulation scheme would also

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likely come into conflict with other national concerns such as industrial policy. Pharmaceuticals constitute the sort of “good jobs” industry that governments try hard to retain or attract. Indeed, Canada gave up its compulsory licensing scheme for drugs in return for an explicit industry commitment to increase local R&D spending. And European policymakers are currently expressing anxiety about the pharmaceutical industry’s tendency to concentrate R&D operations to the United States. It is easy to see how these goals could come into conflict with international price regulation. In Britain, for example, drug companies that spend more on R&D within the country are subject to looser price controls.

IF INTERNATIONAL PRICE REGULATION IS NOT THE SOLUTION, WHAT IS?

Free-riding problems are notoriously difficult to solve. If national governments are unwilling or unable to support R&D collectively through intellectual property rights and the enforcement of price differences, they could, in principle, try other mechanisms – notably public production of pharmaceuticals or taxes/subsidies. But neither seems particularly appealing.

The involvement of the National Institutes of Health in screening for cancer drugs in a more-or-less commercial mode was largely unsuccessful. Nor have the well-intentioned efforts by the WHO to develop treatments and vaccines for tropical diseases worked well.

Taxes and subsidies would surely be dead on arrival. Why would European governments be any more willing to support “American” pharmaceutical companies with an explicit R&D levy than they have been to do so through the far less visible channel of pricing? And how would such a levy be deter-

mined, and on what basis would subsidies be distributed? The experience of international “cooperation” through agreements such as Kyoto or the WTO is not encouraging.

Commissioner McClellan has suggested that “fair” international cost sharing should be based on prices that reflect international income differences. This makes sense, perhaps with some allowance for different national tastes for spending on health care versus other priorities. But it is difficult to see how this could happen through moral suasion in a world market largely dominated by government price setters.

With the right set of institutions, market forces would be capable of reaching a better approximation to the “right” outcome. These would include strong intellectual property rights and tight restrictions on parallel trade, willingness of national governments to confront individual consumers of pharmaceuticals with prices that are at least proportional to those set by manufacturers, greater use of cash subsidies for low-income groups rather than regulated prices, promotion of competitive supply and generic entry, etc. But sadly, such reforms seem unlikely in the countries currently benefiting from free-riding.

In sum, the stakes are enormous, but too many of the stakeholders seem unable to look beyond short-term parochial interests. For current levels of R&D to be sustained, consumers and taxpayers in wealthy countries will have to pay premium prices. Lower prices would mean fewer new drugs, and elected representatives have a responsibility to make this clear. Myopic policies that shift the burden of supporting commercial R&D to future generations or to lower-income countries would be wretched choices. Unfortunately, short political horizons and the difficulty of explaining where our enlightened self-interest lies may make them irresistible choices. ■

WHAT I WOULD DO

BY DAVID BALTIMORE

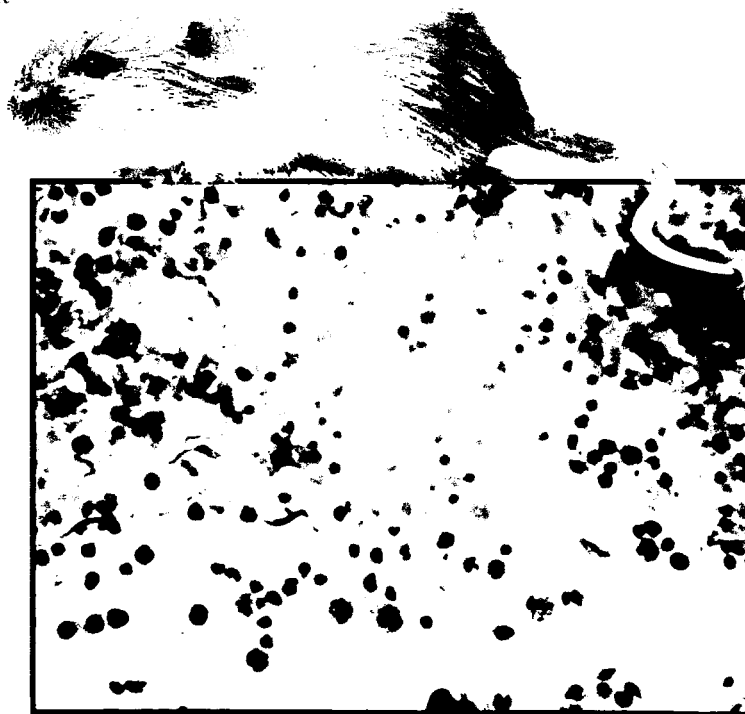
The Center for Accelerating Medical Solutions (CAMS) is asking researchers from a variety of fields to suggest novel ways in which the system for producing medical treatments can be made more effective. Here, David Baltimore, the Nobel Prize-winning virologist who is now president of Cal Tech and a member of the CAMS board sketches one approach.

— Peter Passell

Medical science has produced miraculous treatments for many diseases in recent years, but certain types remain intractable. Many cancers cannot be treated. Autoimmune diseases remain a plague. We can prevent many infectious diseases by vaccination – but not AIDS, tuberculosis or malaria. Medical science continues to work on these problems, but the longer we go without progress, the more we should be saying, “Perhaps these problems need a revolutionary approach.”

The Bill & Melinda Gates Foundation has set up special grants for “grand challenge” approaches to the killers of the less-developed world, primarily the three infectious diseases that have resisted efforts to design a vaccine. This represents recognition of the difficulty of dealing with these particular agents as well as the difficulty of doing medicine in circumstances where the infrastructure and resources for delivering care are very limited.

I suggest one general approach to these problems that would be revolutionary and which poses great challenges, but could pro-



vide new hope for dealing with these intractable problems. It derives from the insight that untreatable cancers – particularly solid tumors and recalcitrant infectious diseases – have one characteristic in common: they

WHAT I WOULD DO

progress even though the immune system is trying its best to mount a defense against them. They slip through our defenses using many strategies – too many to list here. Suffice it to say that there is often a potentially effective immune response, but it lacks the power to totally control the pathogenic process.

Untreatable cancers have one characteristic in common: they progress even though the immune system is trying its best to mount a defense against them.

It is conventional wisdom that dietary supplements, positive thinking, stress control and other environmental manipulations can increase the effectiveness of the immune system, but none of these activities is of documented value. However, the immune system is genetically controlled and it is possible to manipulate its mechanisms using gene-therapy methods. All immune cells derive from so-called hematopoietic stem cells – cells found in adults in the bone marrow. So the gene therapy could be performed on bone marrow stem cells, mobilizing the cells from the bone into the blood by standard methods and allowing them to be harvested from the blood.

The procedure for modifying the genes of bone marrow stem cells has been well established in mice. The most efficient way to do it is to bring new genes into the cells using a virus as a carrier or vector. We and others

have achieved especially high efficiency using so-called lentivirus vectors as carriers of the new genes. Lentiviruses are the class of viruses that include HIV, but the vector is completely denuded of any genes that might cause disease and is purely a carrier of the modifying genes.

We have had good results with two kinds of genes, ones that encode negative regulators called small, interfering RNAs (siRNAs) and ones that encode the business end of certain immune cells called T-cell receptor (TCR) genes. There are other genes that could produce a therapeutic effect and could be used in such a protocol.

If siRNAs and TCRs have given such good results, why is such a gene therapy protocol considered a grand challenge? Because the method being proposed has never been used therapeutically in humans, and would create a number of potential dangers. For instance, the vector brings genes into cells by integrating its DNA with the cell's DNA. However, it integrates randomly and could integrate near a cancer-causing gene, activate it and produce a cancer cell.

This is not a theoretical issue: in a clinical trial using a virus related to the lentivirus, just such an integration potential was found. If this possibility can be circumvented, other problems loom. And if they can be solved, to export this methodology to the less-developed world would mean greatly simplifying it to drive the cost way down.

There are a few laboratories working along these lines. But I would encourage the National Institutes of Health to identify a series of really difficult but potentially valuable methodologies, like this, and to encourage their development with funds targeted to grand challenges that have huge payoffs. That could accelerate medical solutions to our most feared diseases. 

BIGGER AND BETTER

Final preparations are underway for the 7th Annual Milken Institute Global Conference, April 26-28, 2004, at the Beverly Hilton Hotel in Los Angeles. The event brings together scientists, business executives, journalists and academics to deliberate crucial social, political and economic issues. Register by March 26 and receive a \$400 discount off the regular fee of \$1,995. For info call 310-570-4605 or go to www.milkeninstitute.org/gc2004.

GO LOS ANGELES

The Milken Institute has been chosen by the City of Los Angeles to lead a year-long project to create a snapshot of the Los Angeles economy and design strategies for maintaining the city's vitality. The analysis will focus on ways to channel private funds into local businesses, to improve the efficacy of job-training, and to attract top-tier industries to keep Los Angeles competitive with other parts of the country.

SUSTAINABLE GROWTH

The second annual California-Israel Eco-Technology Partnership Forum, held on October 16, 2003, included an impressive group of participants, including former Israeli Prime Minister Shimon Peres. The event, sponsored by the Israel Economic Mission and hosted by the Milken Institute, featured panel discussions with leaders in water and energy technology from California and Israel. To view a summary, visit www.milkeninstitute.org.

ASIAN BOND FORUM

The Milken Institute and the University of Hong Kong's Asian Institute of International Financial Law jointly hosted the first annual Asian Bond Market Forum in Hong Kong, November 11-14, 2003. Participants came from a variety of research, government and private-sector organizations including the IMF, World Bank, Asian Development Bank, Federal Home Loan Bank of Chicago, Goldman Sachs, Deutsche Bank and China Construction Bank. For a summary of the proceedings, visit www.milkeninstitute.org.

CALIFORNIA DREAMIN'

California's huge store of talented workers, world-class universities and risk-taking entrepreneurs will return the state economy to global leadership. That was the consensus of business leaders, government officials and academic experts who spoke at the 5th annual California State of the State Conference on October 30, 2003 in Los Angeles. Visit www.milkeninstitute.org to view a summary.

CAMS ADDS TALENT

Sarah Caddick, an award-winning medical researcher, has been named executive vice president of the Milken Institute's Center for Accelerating Medical Solutions. Caddick comes to CAMS from the Wadsworth Foundation, an organization dedicated to finding a cure for multiple sclerosis, where she had been executive director. For more information, visit www.fastercures.org. **M**

L I S T S

In 1985, physicians prescribed 1.09 drugs for every office visit. Fourteen years later, the figure reached 1.46 per office visit.

The increased volume of prescriptions accounted for 39 percent of the 2000-2001 rise in retail spending, while price hikes accounted for 37 percent. A shift toward the use of higher priced drugs from pharma's larder accounted for the rest.

Half the increase in prescription revenues in 2001 is explained by sales of just 27 drugs,

with Lipitor, Imitrex, Fluoxetine, Zocor, Vioxx, Nexium, Advair, Protonix, OxyContin, Zyprexa, Celexa, Actos, Celebrex and Prevacid leading the pack.

Generics topped sales in four of the 30 therapeutic categories in 2001: atenolol (blood pressure), albuterol (asthma), alprazolam (anxiety) and tamoxifen (breast cancer).

TOP 25 DRUGS IN THE UNITED STATES, 2001

RANK	NAME OF DRUG	TYPE OF DRUG	2001 SALES (MILLIONS)	2001 AVERAGE PRICE PER PRESCRIPTION	PERCENT CHANGE IN SALES	PERCENT CHANGE IN AVERAGE PRICE	PERCENT CHANGE IN UTILIZATION
1	Lipitor	Cholesterol Reducer	\$4,517.5	\$84.96	22.3%	2.9%	18.9%
2	Prilosec	Ant ulcerant	\$3,999.0	\$143.68	-2.5%	3.7%	-6.0%
3	Prevacid	Ant ulcerant	\$3,195.8	\$133.20	12.8%	5.7%	6.7%
4	Zocor	Cholesterol Reducer	\$2,739.2	\$120.82	24.1%	7.5%	15.4%
5	Celebrex	Anti arthritic	\$2,387.2	\$97.32	18.4%	9.4%	8.2%
6	Zoloft	Antidepressant	\$2,152.5	\$83.34	13.9%	3.5%	10.0%
7	Paxil	Antidepressant	\$2,124.1	\$84.91	17.5%	8.0%	8.8%
8	Vioxx	Anti arthritic	\$2,026.2	\$85.44	33.5%	7.9%	23.7%
9	Prozac	Antidepressant	\$1,993.8	\$121.52	-22.3%	10.6%	-29.8%
10	Augmentin	Enhanced Antibiotic	\$1,873.1	\$81.54	18.2%	9.0%	8.5%
11	Claritin	Oral Antihistamine	\$1,869.7	\$73.80	12.1%	8.4%	3.4%
12	Zyprexa	Antipsychotic	\$1,823.4	\$284.07	28.6%	5.9%	21.3%
13	Norvasc	Calcium Blocker	\$1,766.5	\$58.38	10.6%	1.7%	8.8%
14	Glucophage	Oral Diabetes	\$1,734.4	\$72.06	6.5%	14.4%	-6.9%
15	Oxycontin	Narcotic Painkiller	\$1,486.0	\$218.08	41.1%	15.4%	22.3%
16	Neurontin	Antiseizure	\$1,485.7	\$112.03	31.3%	4.4%	25.8%
17	Pravachol	Cholesterol Reducer	\$1,420.1	\$104.28	18.0%	7.5%	9.7%
18	Premarin Tabs	Estrogen Therapy	\$1,240.4	\$30.41	8.2%	11.1%	-2.6%
19	Hydrocodone/ Apap*	Narcotic Painkiller	\$1,196.5	\$15.45	28.0%	13.9%	12.3%
20	Risperdal	Antipsychotic	\$1,188.3	\$163.97	23.8%	6.7%	16.0%
21	Wellbutrin SR	Antidepressant	\$1,185.9	\$91.55	39.4%	6.6%	30.7%
22	Allegra	Oral Antihistamine	\$1,164.7	\$60.10	43.8%	10.9%	29.6%
23	Effexor XR	Antidepressant	\$1,151.4	\$103.12	41.1%	7.3%	31.5%
24	Celexa	Antidepressant	\$1,139.7	\$71.70	54.5%	3.8%	48.8%
25	Zithromax Z-Pak	Broad Antibiotic	\$1,074.7	\$42.21	11.8%	2.9%	8.6%

*Generic drug
SOURCE: American Institutes for Research

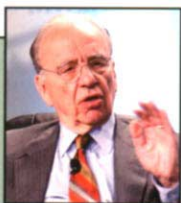
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